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E<small>DITORIAL</small>

The role of statistical significance in health risk assessment and in the decision-making process

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Dear Editor,

We appreciated the article by Filippini and Vinceti [1]. It highlights one of the most important recent changes in scientific methodology: the role of "statistical significance" "in the establishment of causal relations in science, including toxicology and biomedical sciences […] psychological and economic research" [1]. The authors claim that "a complete demise of this simplistic approach appears fully justified in both public law and health risk assessment in favour of a more challenging but methodologically correct method based on the comprehensive assessment of the strengths and limitations of all the available evidence" and they stress that "statistical significance testing has been the pillar and the tenet of risk assessment and biostatistics for decades" [1].

When studying causal relations between two variables in a population, for instance between a possible cancerogenic agent and cancer, the best method is to study the entire population. This allows us to calculate the relative risk (RR) related to the exposure, comparing the absolute risk of cancer in the population exposed to the possible cancerogenic agent and the absolute risk of cancer in the population not exposed to this agent.

When the population is large, it is not always possible to study the entire population, so we have to calculate the relative risk of cancer by comparing the absolute risk of cancer in a population sample exposed to the possible cancerogenic agent and in a population sample not exposed to this agent. In so doing, we obtain a relative risk (RR), for instance RR = 3, meaning that in the sample studied, the frequency of cancer is three times more frequent in the sample exposed to the agent.

Is this relative risk representative of the population or is this result related to population sampling? In other words, is this result due to the sampling variation around the true value or could it be representative of the true value in the population?

"Statistical significance" is a way to try to answer this question.

It starts from the hypothesis (the so-called "null hypothesis") that in the population there is no relation between the two variables considered (the possible cancerogenic agent and the cancer, *i.e.* that the RR = 1 and that the possible cancerogenic agent is not cancerogenic). If this hypothesis is true, what is the probability (p-value) of obtaining a result, such as the one observed in the population sample (RR:3) or more distant from the above hypothesis?

If this probability is low, traditionally < 0.05 (< 5%), the hypothesis that the real value of relative risk in the population is 1, that is, that the result observed (RR = 3) is due to sampling variability, is not considered a valid explanation, the "null hypothesis" is refused, and the result (RR = 3) is considered "statistically significant". Conversely, if the p-value is > 0.05, the hypothesis that the real value in the population is 1, i.e. that the sampling variability is a valid explanation of the observed result, it is "not refused" and the observed result is considered "not statistically significant".

It has been proposed to replace the term "significance" with "compatibility" and "significance" test with "hypothesis" test, in order to emphasise that hypothesis tests evaluate the compatibility between a hypothesis or a model and observed data [2, 3]. Specifically, it is important to report that: if the test's hypothesis is true, the probability to obtain results, that are equally or less compatible with (or equally or more distant from) the above hypothesis than those observed, is p.

We would like to make two observations about the proposal of the authors and many scientists to abandon the use of "statistical significance" [4].

First, "statistical significance", as defined in relation to null hypothesis statistical testing, has been proposed to prevent false positive results, that is, considering that there is an association between two variables studied in a population sample, when this association is absent in the population and the result observed in the population sample is due to sampling fluctuation around the true value. Therefore, we have to be aware that completely abandoning "statistical significance" may lead to an increase in false positive results [5] and to a decrease in false negative results. Anyway, the best method to prevent false positive and false negative results is to increase the sample size. Increasing the sample size decreases the probability of refusing a result when that result is true and decreases the probability of not refusing a result when it is false.

"How feasible is it to abandon statistical significance?" [6]. It is feasible by simply reporting the results of clinical trials as relative and absolute risk

between the treated group and the untreated group, without doing the hypothesis test. These results, if derived from well-designed trials (e.g. prospective double-blind randomized trial between two homogeneous groups) "count as evidence" [5] of association between two variables in a population. The only way to determine whether a result is due to sample variability is to repeat the trial and to increase the sample size.

Secondly, the American Statistical Association (ASA) released a statement on statistical significance in 2016 which states that statistical significance "is not equivalent to scientific, human, or economic significance" [7], meaning that a scientific result may be important or "significant", even if it is not "statistically significant".

We want to stress the importance of this concept, because, in patient-centred medicine, the patient must be put at the centre of the decision-making process. The patient must decide if a scientific result is significant for him/her, considering his/her needs and values. Similarly, in a decision-making process, we have to put the decision-maker (e.g., a public health agency) at the centre of the decision-making process. The use of "statistical significance", as a means to decide if a result is scientifically important or not, does not put the decision-maker at the centre of the decision-making process, because the test discriminates between significant and non-significant results before the evaluation of the decision-maker. This implies that reporting the results of a scientific study, without classifying them as "statistically significant or not statistically significant", may put the decision-maker at the centre of the decision-making process, promoting patient-centred medicine [8].

The signatories of the petition for retiring statistical significance [4] were asked about their intentions: specifically, about how likely they are to use the concept of "statistical significance" in their future publications [5]. Forty-two percent declared they are neutral or likely to use it in future publications, and 58% declared that they expect to never to use it again or they said it would be unlikely they would use it in future publications. The use of hypothesis testing in publications depends on several factors, first of all on the editor's willingness to accept both studies in which it is used and studies in which the hypothesis test is not used. We agree that it is important to "promote more education among researchers and users of scientific evidence" [6] about statistical significance. At the same time, we agree with ASA, that it is important to "open a fresh discussion and draw renewed and vigorous attention to changing the practice of science" [7].

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contribution

MP conceived and drafted the manuscript. MAM revised the manuscript, especially the statistical section. All authors have read and approved the latest version of the paper for publication.

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COVID-19

Association between physical activity and risk of COVID-19 infection or clinical outcomes of the patients with COVID-19: A systematic review and meta-analysis

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Keywords

Exercise • COVID-19 • SARS-CoV-2 • Systematic Review • Meta-analysis

Summary

Objective. *The COVID-19 pandemic has caused serious consequences for global health and economy. The important question is whether the level of physical activity might influence the risk of COVID-19 incidence or clinical outcomes, including the severity or mortality of infected patients. The objective of this systematic review and meta-analysis is to evaluate the association between sufficient physical activity and incidence, hospitalization, severity, recovery, and mortality of COVID-19.*

Methods. *A systematic search of Web of Sciences, PubMed, and Scopus between December 2019 and November 2021 was conducted. Studies were screened based on the inclusion criteria, i.e. observational studies (case-control, prospective or retrospective longitudinal designs, and cross-sectional studies) which have determined the association of physical activity, exercise, sports participation, or sedentary behavior with COVID-19 incidence or outcomes, including mortality, severity, recovery and hospi-*

talization in healthy population or population with any specific comorbidity.

Results. *Based on eligibility criteria, 27 articles were finally included in the qualitative synthesis. The meta-analysis of five studies evaluating the association of physical activity and COVID-19 mortality showed a weighted OR of OR of 0.61 (CI 95%: 0.50-0.75) with heterogeneity ($I^2 = 45.8\%$, $P < 0.001$) and in seven studies regarding physical activity and COVID-19 hospitalization, weighted OR was 0.541 (CI 95%: 0.491-0.595) with heterogeneity ($I^2 = 81.7\%$, $P < 0.001$).*

Conclusion. *Participating in sufficient physical activity might decrease COVID-19 related COVID-19-related hospitalization and mortality. Developing programs to increase physical activity during the COVID-19 pandemic might be an appropriate health strategy.*

Introduction

The pandemic of COVID-19 has challenged world health systems, economy, and social lifestyles. As a consequence of the frequent lockdowns, public avoidance of social activities and the closure of sports clubs and public venues, physical activity level appears to have declined among different populations [1]. This may lead to short and long-term public health consequences, and an increase in the burden of non-communicable diseases [2]. Participating in regular physical activity improves mental and physical health [3]. Improvement in immunity state in various conditions including cardiovascular disease, insulin resistance state, dementia, and cancer have been indicated in individuals participating in regular exercise [4]. Moderate-intensity physical activity reduces the incidence, prognosis, and severity of viral respiratory infections with several mechanisms affecting the immune system [4-7]. Natural killer (NK) Cells, salivary IgA concentrations, neutrophils, and stress hormones are increased and

Th1/Th2 cell responses are regulated via engaging in moderate-intensity physical activity [6].
COVID-19 clinical manifestations consist of a variable spectrum including asymptomatic, mild to moderate, and severe intensity. It is assumed that physical activity may boost immunity in COVID-19 patients and reduce severe outcomes [7]. On the one hand, the physical activity leve&l of the community has been reduced inevitably, due to the COVID-19 preventive protocols (including staying at home, social distancing programs, etc.). On the other hand, physical activity may potentially reduce the incidence of COVID-19 and improve the consequences in COVID-19 patients. A few studies assessing the effects of physical activity on COVID-19 severity, morbidity, mortality, and hospitalization have been conducted [7-9]. Currently, no systematic review has been accomplished in this domain. Indeed, by conducting this systematic review and meta-analysis, we aimed to demonstrate whether if engaging in physical activity is beneficial in COVID-19 control strategies and recommend the policymakers develop proper action plans regarding physical activity in

the community. [10]. The objective of this study was to perform a systematic review and meta-analysis evaluating the association between physical activity and the risk of COVID-19 infection or clinical outcomes of the patients with COVID-19.

Methods

PROTOCOL

The current systematic review and meta-analysis were accomplished according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [11]. The complete study protocol was registered on PROSPERO (protocol number: CRD42021291451).

SEARCH STRATEGY AND INFORMATION SOURCES

Electronic resources including Web of Sciences, PubMed, and Scopus between December 2019 and November 2021 were searched systematically. In the next stage, in the related studies, references were assessed. Search keywords were as follows: "physical activity" OR "exercise" OR "physical inactivity" OR "sedentary behavior" OR "lifestyle" OR "sports" in combination with "COVID-19" OR "SARS-CoV-2".

ELIGIBILITY CRITERIA AND STUDY SELECTION

Inclusion criteria were: 1) observational studies including case-control, prospective or retrospective longitudinal designs, and cross-sectional studies, 2) studies conducted in healthy population or population with any specific comorbidity, 3) COVID-19 patients were detected via diagnostic tests, hospital reports, or deterministic signs or symptoms, 4) studies have tested the association of physical activity, exercise, sports participation, or sedentary behavior with risk of incidence or COVID-19 outcomes, including mortality, severity, recovery, and hospitalization.
Studies qualified based on inclusion criteria were evaluated. Qualitative studies, reviews, commentaries, and editorials were excluded. The studies were not excluded based on the assessment method of physical activity level or diagnostic method of COVID-19 in patients. The screening and study selection process was conducted via wotwo independent reviewers (B.T. & M.S.) and any disagreement was discussed until a settlement was achieved. If no agreement was attained, a third reviewer (B.M.) arbitrated the process.

DATA EXTRACTION

Two independent reviewers (B.T. & M.S.), extracted data by applying a standardized data extraction form. Data extraction form consisted of study characteristics including the name of the first author, sample size, physical activity measure, and assessment tool, outcome definition and assessment method, study design, and reported association of physical activity, exercise, sports participation, or sedentary behavior with COVID-19 outcome. A third

reviewer (B.M.) evaluated any disparities between results and disagreements were discussed between reviewers until achieving a final agreement.

QUALITY ASSESSMENTS OF STUDIES

Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional, case series, and cohort studies were applied for the quality assessment of studies (Supplementary Table I) [12]. Two reviewers (B.T. & M.S.), applied JBI, and the results were assessed with a third reviewer (B.M). Any disagreement was discussed to achieve a settlement.

STATISTICAL ANALYSIS

Meta-analysis was conducted on studies based on inclusion and exclusion criteria and eligibility of homogenous assessment methods for physical activity and clinical outcomes. Association between physical activity and clinical outcomes including odds ratio, risk ratio, hazards ratio, incidence risk ratio, prevalence ratio, Beta, and correlation coefficient were recorded. Studies containing odds ratio, risk ratio, hazards ratio, incidence risk ratio, and prevalence ratio were meta-analyzed, via STATA (version 13). A random-effect model was applied to evaluate associations between physical activity and clinical outcomes. Assessments of the studies' heterogeneity were via determining the Q-statistic and the I-squared index. A heterogeneity more than 75% was defined as high, and below 40% was insignificant.

Results

Results of a systematic search through Web of Sciences, PubMed, and Scopus databases for published studies consisted of 6485 studies. After duplicate removal, 3332 studies were evaluated in the primary screening process for subject relativity, and 67 studies were appropriate for complementary full-text assessment. After assessing the study according to eligibility criteria, 27 articles met the inclusion criteria. PRISMA flowchart is illustrated in Figure 1.
Study characteristics have been reviewed and presented in Table I. Among 27 studies included, patients with COVID-19 were assessed about engaging in physical activity, sports participation, and sedentary behavior.

PHYSICAL ACTIVITY AND COVID-19 INFECTION

Twelve studies have assessed the association between physical activity and COVID-19 infection. Gao et al. suggested that engaging in physical activity more than 5 times a week increased the risk of COVID-19 infection [19]. In studies by Huang et al. and Hamer et al., a sedentary lifestyle and physical inactivity have been proposed as risk factors for COVID-19 infection [20, 22]. Cho et al. indicated that increasing physical activity level per each standard deviation in MET-min/week might reduce the risk of COVID-19 infection [16]. Based on Lee et al. study engaging in sufficient physical activity (aerobic and strengthening exercises) reduces the probability

Fig. 1. Flow diagram of systematic literature search on physical activity and COVID-19 outcomes.

Records identified through database searching:

PubMed, Web of Science, Scopus, Google Scholar,

N= 6485

Additional records identified through other sources

From citations in the selected papers

N= 15

Records after duplicates removed
(n = 3332)

Records screened
(n = 3332)

Records excluded, with reasons:

Not related: 3265

Full-text articles assessed for eligibility
(n =67)

Full-text articles excluded, with reasons:

Similar content with different titles (n=1)

Type of the study (n=20)

PA not assessed (n=11)

COVID-19 outcome not assessed (n=8)

6

Studies included in qualitative synthesis
(n = 27)

Studies included in quantitative synthesis (meta-analysis)
(Hospitalization n =7, Mortality, n=5)

of infection compared to inactive individuals (2.6% *vs* 3.1%) [24]. Country-level physical activity reduced the risk of COVID-19 disease in a study by Cunningham et al. [17]. Rowlands et al. suggested that moderate to vigorous physical activity and total physical activity level have no correlations with COVID-19 infection [32]. In a study by Zhang et al. increased physical activity level (based on an acceleration vector scale) reduced the risk of COVID-19 overall infection and outpatients [36]. Bielik et al. did not demonstrate a decreased risk of COVID-19 incidence among cold-water swimmers (physically active individuals). However, an increased probability of asymptomatic COVID-19 and decreased probability of re-infection exceeding twice annually was demonstrated among swimmers [15]. Marcus et al. indicated a reduced risk of incidence of SARS-CoV-2 infection symptoms among individuals participating in the weekly exercise [27]. Also, Nguyen et al. proved that physical activity reduced COVID-19-like symptoms' likelihood [28].

PHYSICAL ACTIVITY AND RISK OF COVID-19 RELATED HOSPITALIZATION

Seven studies evaluated the association between physical activity and the risk of hospitalization in patients with COVID-19. An accelerometer was used as an objective physical activity assessment method in a study by Li et al. [25]. No correlation was detected between physical activity predicted genetically (each standard deviation increase) with hospitalization due to COVID-19 [25]. Subjective methods including the international physical activity questionnaire (IPAQ) short version [18, 23], Exercise Vital Sign (EVS) [7, 26], and membership in the sports medicine insurance system [8] were applied in the studies to assess physical activity. De Souza et al. showed a 37.6% reduction in the prevalence of COVID-19 related hospitalization in individuals engaging in sufficient physical activity [18]. In Latorre-Román et al. study, engaging in more than 150 minutes of moderate physical activity per week indicated a negative relation with hospitalization [23].

Tab. I. Characteristics of studies on the association between regular physical activity and clinical outcomes of the patients with COVID-19.

Results	Outcome	PA assessment tool	Exercise, physical activity, sedentary behavior, etc.	Participants	Study design (type/ registration time)	Study and country
Among physically active individuals decreased mortality was detected (RR: 0.70, 95% CI: 0.54-0.89)	Mortality	Questionnaire (IPAQ short version)	Physical activity	468,569 participants (mean age: 56.5 ± 8.1)	Cohort study/ March to June 2020	Ahmadi et al. [13] (2021) United Kingdom
Individuals engaging in regular physical activity have a 2.7-time faster recovery process compared to inactive individuals (p = 0.00)	Recovery time	12 multiple choice questionnaire using a self-rated scale	Fulfilling WHO physical activity recommendation (150 min/w)	215 (mean age: 36.3 ± 16.2 years) COVID-19 infected participants	Cross sectional	Boukelia & Alataibi [14] (2020) Kingdom of Saudi Arabia
Among cold-water swimmers (physically active individuals) lower probability for COVID-19 incidence was not detected (RR:1.07, 95% CI: 0.71-1.62) but increased probability of asymptomatic COVID-19 (RR: 2.32, 95% CI: 0.83-6.44; p < 0.05) was demonstrated	Infection incidence, re-infection, and less severe forms	Adapted version of Questionnaire (IPAQ short version)	Physical activity	2343 participants [male mean age: 30.5 (29.7-31.3) female mean age:35.1 (34.4-35.8)]	Cross sectional study/7 December-18 December 2020	Bielik et al. [15] (2021) Slovak Republic
Moderate to vigorous physical activity reduced morbidity (adjusted OR:0.90, 95% CI, 0.86-0.95) and mortality (adjusted OR, 0.47; 95% CI, 0.26-0.87) in patients with COVID-19. Each standard deviation increase in physical activity (MET-min/week) reduced risk of infection and mortality of COVID-19 by 4% and 35%, respectively	Morbidity and mortality	Self-reported questionnaire	Leisure time physical activity (Moderate to vigorous PA or MVPA)	6289 COVID-19 infected participants (mean age: 50.7 ± 14.3 years) & 125,772 Healthy individuals (mean age: 50.7 ± 14.3 y)	Retrospective observational study (Case-Control Study)/ January 1-July 16, 2020	Cho et al. [16] (2021) South Korea
Negative associations between county-level physical activity and COVID-19 infection (r = -0.14) or mortality (r = -0.23) were detected	Mortality	Website databank via a questionnaire	Physical Activity	3142 counties of USA	Cross sectional/ January 20-November 30, 2020	Cunningham [17] (2021) United States
Engaging in regular physical activity (moderate physical activity for at least 150 minutes weekly or vigorous physical activity for at 75 minutes weekly reduces hospitalizations prevalence among COVID-19 patients (Adjusted PR: 0.65; P = 0.046)	Hospitalization	Online questionnaire (IPAQ short version)	Physical Activity	938 survivors and fully recovered patients infected with COVID-19	Cross sectional/ June-August, 2020 (IPAQ short version)]	de Souza et al. [18] (2021) Brazil

▶

Tab. I. *Continues.*

Results	Outcome	PA assessment tool	Exercise, physical activity, sedentary behavior, etc.	Participants	Study design (type/ registration time)	Study and country
Having physical activity exceeding 5 time a week increased risk of COVID-19 infection (adjusted OR: 2.05, 95% CI: 1.39-3.02)	COVID-19 diagnosis	Questionnaire	Physical activity (frequency per week in latest 2 months)	105 COVID-19 infected participants (Median age: 55.0 y, IQR: 45.5-66.5) and 210 healthy individuals (Median age: 54.0 y, IQR, 45.0-68.0)	Case-control study/ February 10-March 1, 2020	Gao et al. [19] (2020) Wuhan, China
Regular sports participation significantly reduced severe outcomes (OR: 0.67, 95% CI: 0.46-0.99)	Hospitalization or death (severe outcome)	Membership in the Sports Medicine Insurance system of Tehran province	Regular sports participation	4,694 (mean age: 42.31 ± 11 years) COVID-19 infected participant	Cross sectional/ February 20-April 20, 2020	Halabchi et al. [8] (2020) Iran
COVID-19 infection risk was augmented in physical inactivity (Adjusted RR: 1.32, 95% CI: 1.10-1.58)	COVID-19 diagnosis	Questionnaire (IPAQ short version)	Physical inactivity	387,109 (mean age: 56.2 ± 8 y) including 760 COVID-19 infected participants	Prospective cohort/March 16-April 26, 2020	Hamer et al. [20] (2020) UK
Low physical activity increased COVID-19 mortality compared to high physical activity (OR:1.41, 95% CI: 1.09-1.83)	Mortality	Questionnaire (IPAQ short version)	Physical activity	259 397 participants	Prospective cohort study/16 March 2020-27 February, 2021	Hamrouni et al. [21] (2021) UK
Sedentary lifestyle increases likelihood of COVID-19 infection (OR: 36.05, 95% CI: 3.44-377.44). Low physical activity increases duration of hospital stay(OR: 6.67, 95% CI: 1.61-27.61	Risk of infection/ Length of hospital stay	Questionnaire (IPAQ short version)	Physical activity based on MET. Minutes/w	431(228 healthy, 203 COVID-19 infected participants)	Retrospective cohort	Huang et al. [22] (2020) China
Engaging in moderate physical activity more than 150 minutes weekly reduces the risk of hospitalization (RR: 0.24, 95% CI: 0.05-1.04)	Hospitalization	Questionnaire (IPAQ short version	Moderate physical activity	≤ 420 COVID-19 infected participants (Median age: 33 (20-54))	Cross-sectional	Latorre-Román et al. [23] (2021) Spain
Engaging in sufficient physical activity (500-<1000 MET min/week) reduced probability of COVID-19 incidence (aRR: 0.78; 95% CI: 0.66- 0.92), probability of severe infection (aRR: 0.62; 95% CI 0.43-0.90) and mortality (aRR: 0.17; 95% CI: 0.07-0.98) compared to inactivity	Risk of infection, severity, and mortality	Interview based questionnaire	Physical activity	2295 infected participants	Cross-sectional/ January 1 2020-July 31 2020	Lee et al. [24] (2021) South Korea

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Tab. I. *Continues.*

Results	Outcome	PA assessment tool	Exercise, physical activity, sedentary behavior, etc.	Participants	Study design (type/ registration time)	Study and country
Lower risk of COVID-19 infection with severe respiratory manifestation was detected with each standard deviation increase in physical activity estimated genetically (OR: 0.19, 95% CI: 0.05-0.74). However, no correlation was demonstrated with hospitalization due to COVID-19	Severe respiratory COVID-19, COVID-19 hospitalization	Accelerometer-measured PA	Physical activity	Data from 2 genome-wide association studies (GWAS) including 9464 hospitalized patients with COVID-19 and 1,297,281 healthy controls	Cross-sectional (Mendelian randomization study)	Li et al. [25] (2021) UK
Inactive individuals were more likely to be hospitalized due to COVID-19 (adjusted OR: 1.25, 95% CI: 1.03-1.51)	Hospitalization	Exercise Vital Sign (EVS), (self-reported PA)	Physical inactivity for those self-reporting < 10 min of exercise/week	5712 COVID-19 infected participants (mean age: 44.81 ± 5.7)	Retrospective cohort study/ March 3-October 29, 2020	Lobelo et al. [26] (2021) United States
Weekly exercise reduced risk of incidence of SARS-CoV-2 infection's symptoms (OR: 0.57, 95% CI: 0.47-0.70)	SARS-CoV-2 infection incidence	Mobile application	Physical activity	14,335 participants	Prospective cohort study/March 26-May 3, 2020	Marcus et al. [27] (2021) United States and 93 countries outside the US
Physical activity reduced COVID-19-like Symptoms' likelihood (OR: 0.69; p < 0.001)	COVID-19-like Symptoms	Questionnaire (IPAQ short version)	Physical activity	3947 outpatients (mean age: 44.4 ± 17.0 y)	Cross sectional study/14 February to 2 March 2020	Nguyen et al. [28] (2021) Vietnam
Increased prevalence of inadequate physical activity augmented the probability of COVID-19 mortality [Beta (SE): 0.08 (0.0333), p = 0.0127]	Mortality	WHO Global Health Observatory Repository	Insufficient physical activity (not meeting the WHO physical activity recommendations)	Publicly available core health data for 53 sub-Saharan African countries	Cross sectional	Okeahalam et al. [29] (2020) sub-Saharan Africa
No associations between total physical activity and duration of hospital stay due to COVID-19 infection (β = 0.20, 95% CI: -0.48-0.87, p = 0.563), mortality (OR: 0.7, 95% CI: 0.4-1.3, p = 0.272), ICU admission (OR: 0.9, 95% CI: 0.7-1.2, p = 0.459), and need to mechanical ventilation (OR: 0.8, 95% CI: 0.5-1.2, p = 0.214) were detected	Length of hospital stay, mortality, ICU admission, need to mechanical ventilation	Baecke Questionnaire of Habitual Physical Activity	Physical activity	209 hospitalized patients with severe COVID-19 (mean age: 54.9 ± 14.5 y)	Prospective cohort/June 2-October 7, 2020	Pinto et al. [30] (2020) Brazil
Recreational physical activity has an inverse association with mortality rate per 100,000 individuals (r: -0.43, p = 0.02), disease lethality (r: -0.51, P = 0.01), and the accumulated deaths (r: -0.44, p = 0.03)	Accumulated deaths, disease lethality and mortality rate	Data through the Risk Factor Surveillance System for chronic non-communicable diseases (VIGITEL 2019)	Leisure time physical activity (LTPA)	26 Brazilian capitals and the Federal District	Cross-sectional/ January 22, 2021	Pitanga et al. [31] (2021) Brazil

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Tab. I. *Continues.*

Results	Outcome	PA assessment tool	Exercise, physical activity, sedentary behavior, etc.	Participants	Study design (type/ registration time)	Study and country
No associations between moderate to high physical activity or total physical activity level with the COVID-19 infection or severe manifestation of COVID-19 were demonstrated. Increased waking time physical activity reduces the risk (OR, 0.75, 95% CI: 0.61-0.93)	SARS-CoV-2 positivity and COVID-19 severity.	Accelerometer data from Biobank	Physical activity	207 COVID-19 infected participants (including 124 patients with severe infection)	Cross-sectional/ March 16-July 19, 2020	Rowlands et al. [32] (2020) UK
Sedentary lifestyle enhances the mortality due to COVID-19 infection. (Adjusted hazard ratio: 5.91, 95%CI: 1.80-19.41)	Mortality	Rapid Assessment of Physical Activity Scale questionnaire	Baseline physical activity level (BPAL)	520 patients hospitalized COVID-19 infected participants (mean age: 54.6, range: 42.9-64.6)	Retrospective cohort Study/ February 15-April 15, 2020	Salgado-Aranda et al. 33 (2021) Spain
Inactive individuals with COVID-19 have higher risk of hospitalization (OR 2.26; 95% CI: 1.81, 2.83), ICU admission (OR = 1.73; 95% CI: 1.18, 2.55) and mortality (OR 2.49; 95% CI: 1.33, 4.67)	Hospitalization, ICU admission and mortality	Exercise Vital Sign (EVS), (self-reported PA)	Physical inactivity	48440 COVID-19 infected participants (median age: 47)	Retrospective observational study/January 1-October 21, 2020	Sallis et al. [7] (2021) United States
Moderate to vigorous physical activity reduces the COVID-19 severe manifestations (OR: 0.28, p = 0.05)	Severe COVID-19 disease	GPAQ	Physical activity	206 COVID-19 infected participants (mean age: 40.9 ± 11.6 y)	Cross-sectional/ March 20-April 24	Tavakol et al. [9] (2020) Iran
COVID-19 mortality indicated positive correlations with insufficient physical activity (R^2 0.04, p = 0.007)	Mortality	2015/2016 WHO handbooks	Insufficient physical activity	Data from 2015/2016 WHO handbooks	Cross sectional study/August 20, 2020	Wang et al. [34] (2021) 186 countries from Africa (55), Asia/Oceania (45), Europe (45), North/Central America (28), and South America (13)
No associations between insufficient aerobic activity and hospitalization rate (Crude OR 1.06; CI 95%: 0.48, 2.34)	Hospitalization	Periodic Health Assessment Questionnaire	Physical activity	93 hospitalized and 372 ambulatory COVID-19 military personnel (median age = 26)	Case-control study/between March 5, 2020, and March 10, 2021	Webber et al. [35] (2021) United States
Increased physical activity level (based on accelerometer) reduces the risk of COVID-19 overall infection and outpatients [36]. However, no association have been demonstrated between physical activity (based on accelerometer) and inpatients or MVPA (based on touch screen questionnaire) and COVID-19 consequences	Overall COVID-19, inpatients and outpatients	Self-reported moderate-to-vigorous PA (MVPA) and acceleration vector magnitude PA (AMPA)	Physical activity	7187 inpatients and 2307 out patients (mean age: 68.8 ± 9.2 y)	Cross-sectional (Mendelian randomization study)/March 16-June 29,2020	Zhang et al. [36] (2020) UK

▶

Halabchi et al. proposed that hospitalization was 1.49 times less probable among athletes participating in regular sports [8]. Physical inactivity was proposed as a major risk factor for hospitalization due to COVID-19 in Sallis et al. and Lobelo et al. studies [7, 26]. Webber et al. did not show an association of between insufficient aerobic physical activity and COVID-19 hospitalization rate among military personnel [35].

Overall, most studies demonstrated the significant impact of physical activity in reducing hospitalization due to COVID-19. The results of a meta-analysis on seven studies evaluating the association of physical activity and COVID-19 hospitalization showed weighted OR= 0.541 (CI 95%: 0.49-0.6) with heterogeneity ($I^2 = 81.7\%$, P < 0.001) (Fig. 2).

Physical activity and COVID-19 related mortality

Eleven studies evaluated the association of physical activity with mortality in patients with COVID-19. Questionnaires [13, 16, 21, 24, 30, 33], exercise vital signs [7], website databank [17], Global Health Observatory Data Repository [29], and surveillance systems [31, 34] were applied to assess the physical activity status. Cho et al. proposed that the higher physical activity level was associated with lower mortality risk due to COVID-19 [16]. Physical inactivity and sedentary behaviour increased mortality risk in COVID-19 patients [7, 29, 33]. In Cunningham's study, country-level physical activity had a negative correlation with COVID-19 mortality [17] and in Pinto et al. study no associations were detected between work-related physical activity, leisure-time physical activity, sport index, and total activity with mortality [30]. Leisure-time physical activity reduced COVID-19 mortality risk [31]. Ahmadi et al. and Lee et al. indicated decreased mortality among physically active individuals [13, 24]. Hamrouni et al. and Wang et al. demonstrated that low and insufficient physical activity increased COVID-19 mortality [21, 34]. Overall, most studies indicated that sufficient physical activity reduces COVID-19 mortality. The results of a meta-analysis on five studies assessing the association of physical activity and COVID-19 mortality showed a weighted OR of 0.61 (CI 95%: 0.50-0.75) with heterogeneity ($I^2 = 45.8\%$, P < 0.001) (Fig. 3).

PHYSICAL ACTIVITY AND COVID-19 RECOVERY, HOSPITAL STAY, AND SEVERITY

Seven studies evaluated the association of physical activity with COVID-19 recovery, hospital stay, and severity. Alataibi and Boukelia indicated that engaging in regular physical activity leads to 2.7 times faster recovery [14]. Huang et al. suggested that low physical activity increases the duration of hospital stay compared to high-intensity physical activity based on METs [22]. In another study by Pinto et al., no associations were detected between physical activity indexes with the duration of hospital stay, ICU admission, and the necessity of mechanical ventilation [30]. Li et al.

indicated that with each standard deviation increase in physical activity estimated genetically, a lower risk of severe respiratory manifestation in COVID-19 patients was detected [25]. Rowlands et al. proposed that no associations exist between total or moderate to high physical activity and COVID-19 infection with severe manifestation [32]. However, increased daytime physical activity reduced the risk [32]. Tavakol et al. suggested that moderate to vigorous physical activity decreases the probability of severe COVID-19 infection and similar findings was detected in Lee et al. study in individuals engaging in aerobics and strengthening exercises [9, 24].

QUALITY ASSESSMENT

Results for the quality assessment of the studies applying Joanna Briggs Institute (JBI) critical appraisal checklist are illustrated in Supplementary Table II (The tools are illustrated in Supplementary Table I) [12].

Results for quality assessment of the studies applying Joanna Briggs Institute (JBI) critical appraisal checklist for cross sectional studies in Q1 were no in Boukelia and Alataibi (2020), Cunningham (2021), Li et al. (2021), Okeahalam et al. (2020), Pitanga et al. (2021), and Wang et al. (2020) studies. The results of question 2 was no in Pitanga et al. (2021) and Latorre-Román et al. (2021) studies. The results of question 3 was no in Bielik et al. (2021), Latorre-Román et al. (2021), and Wang et al. (2020) studies and unclear in Okeahalam et al. (2020) and Pitanga et al. (2021) studies. The no answer for question 4 was in Okeahalam et al. (2020) and Pitanga et al. (2021) studies, for question 5 in Bielik et al. (2021) and for question 7 in Bielik et al. (2021), Boukelia and Alataibi (2020), Cunningham (2021), de Souza et al. (2021), Latorre-Román et al. (2021), and Sallis et al. (2021) studies. The answers to other questions were yes (Supplementary Table II).

In the cohort studied the negative answer in question 1 was in Hamer et al. (2020), and Lobelo et al. (2021) and Marcus et al. (2021) studies and in question 2 was in Pinto et al. (2020) and Lobelo et al. (2021) studies. Question 8 and 10 was unclear in all cohort studies. In case-control studies, results of question 8 was no in all studies and in question 9 unclear in all studies (Supplementary Table II).

Discussion

A high proportion of studies indicated that engaging in physical activity might reduce the risk of COVID-19 infection, hospitalization, and mortality due to COVID-19. The results of the meta-analysis regarding the association of physical activity and COVID-19 hospitalization and mortality showed statistically meaningful differences in favour of physically active patients.

In a systematic review by Song et al., the association between physical activity and influenza/pneumonia was evaluated [37]. The overall conclusion of the studies indicated that engaging in regular exercise might be a protective factor against influenza-related infection in

Fig. 2. Forest plot of the association between physical activity and COVID-19 hospitalization.
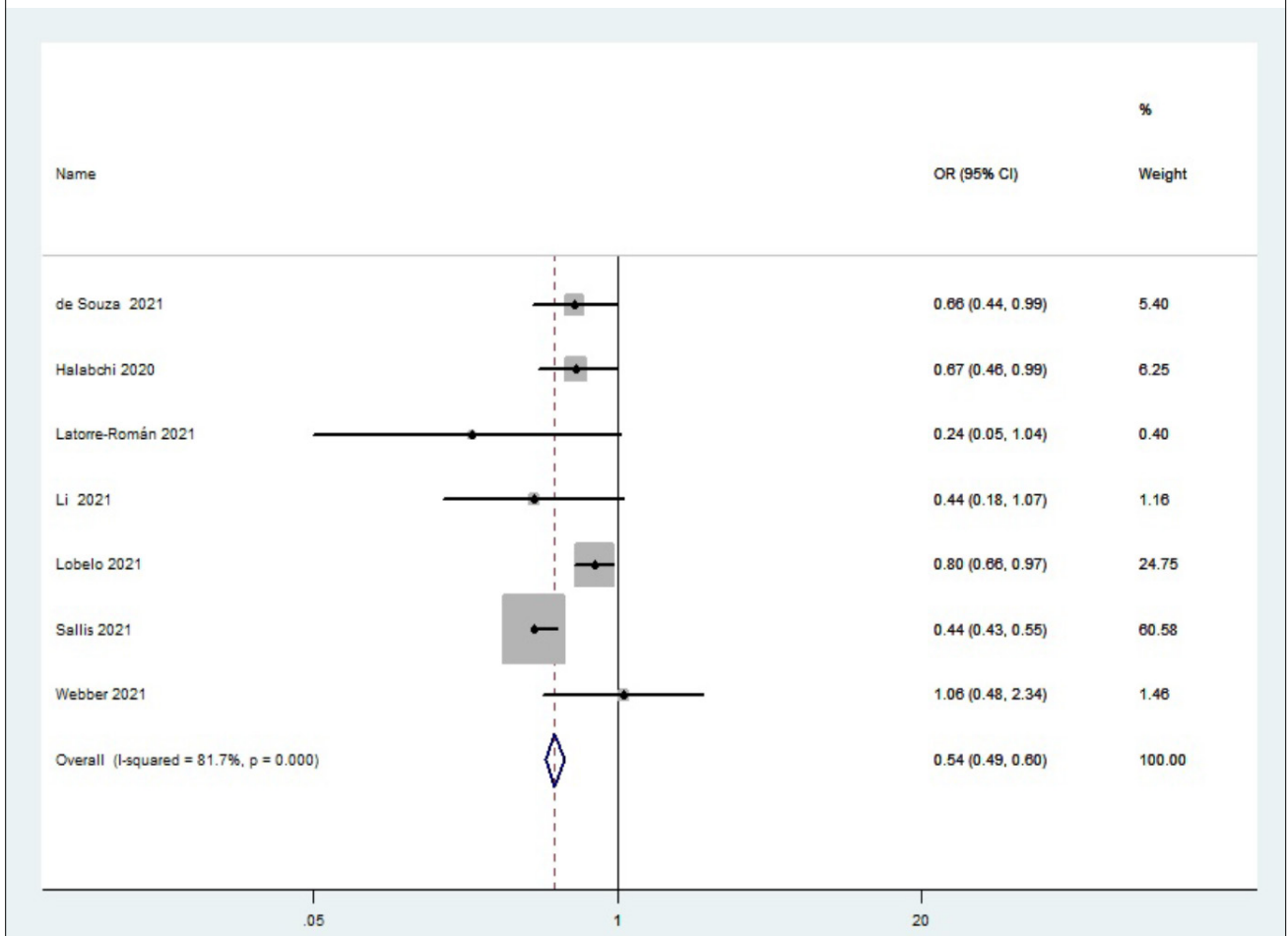
older populations [37]. Simultaneously, the benefits of engaging in Asian martial arts on the immunological state of the older individuals were suggested [37].

It has been proposed that engaging in regular exercise programs might be a protective factor against the risk of viral infection, duration, and clinical outcome of the viral diseases [38]. Higher level of habitual physical activity reduces the risk of community-acquired infectious disease by about 31% and reduces the risk of infectious disease mortality by about 37% [39].

Engaging in moderate- to vigorous-intensity exercise programs regularly improve the respiratory system's function and a 20-30 percent reduction in upper respiratory infections is detected [6]. In a study by Nienman et al., physical fitness level and number of aerobic exercise sessions during the week were inversely correlated to the duration and severity of upper respiratory tract infection [40]. Individuals exercising ≥ 5 days/week indicated a 43% reduction in upper respiratory tract infection duration compared to sedentary individuals [40]. Individuals exercising ≥ 5 days/week indicated about a 43% reduction in duration of upper respiratory tract infection compared to sedentary individuals [40]. Physical fitness can also reduce COVID-19 related risk factors including hypertension, diabetes, cardiovascular diseases.[41].

Engaging in moderate intensity exercise regularly, balances immunity function in inflammatory related disease including type 2 diabetes, obesity, and cardiovascular diseases, and stabilizes hallmarks of immunosenescence [42]. Simultaneously, the positive effect of exercise on the function of different leukocyte subtypes and the arrangement of the T cell compartment havehas been shown leading to improved adaptive immunity [42]. Moderate intensity exercise shifts immunity responses towards a T-helper type 1 pattern and decreases the probability of infection [43]. In a study by Terra et al., 12 weeks of exercise in mice led to increased interferon-gamma (IFN-γ) and TNF-α levels and a reduction in IL-4 and IL-10 levels. Based on the results of the systematic review by Chastin et al., physical activity-increasing interventions increase CD4 cell counts and salivary immunoglobulin A concentration and reduce neutrophil counts [39].

Among individuals infected with COVID-19, the severe clinical presentation of the disease in some patients appears approximately 7 to 10 days after the onset. This delayed manifestation of COVID-19 is a consequence of the over-activity of the immune system "cytokine storm syndrome" aiming lungs [4]. The anti-inflammatory effect of exercise is a consequence of increased mediators including IL-1 receptor antagonist, IL-10, and IL-6 [44].

Fig. 3. Forest plot of the association between physical activity and COVID-19 mortality.

Name	OR (95% CI)	% Weight
Ahmadi 2021	0.70 (0.54, 0.89)	64.90
Cho 2021	0.47 (0.26, 0.87)	11.11
Lee 2021	0.17 (0.07, 0.98)	2.33
Pinto 2020	0.70 (0.40, 1.30)	11.66
Sallis 2021	0.40 (0.21, 0.75)	10.00
Overall (I-squared = 45.8%, p = 0.117)	0.61 (0.50, 0.75)	100.00
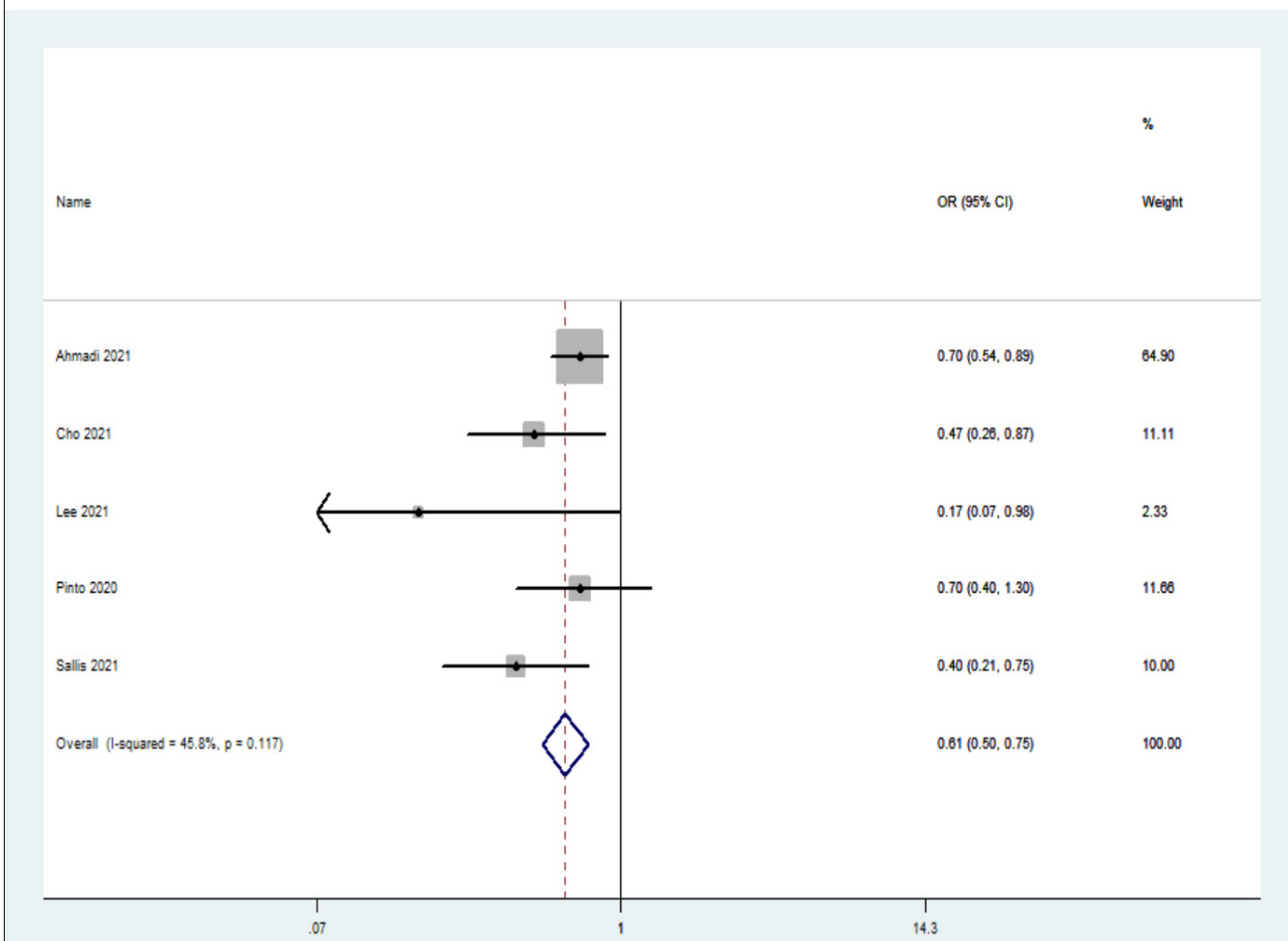
During exercise, skeletal muscles produce and release IL-6, which is one of the leading determinants of exercise's anti-inflammatory mechanism [45]. Another suggested anti-inflammatory effect of exercise is the reduction of Toll-like receptor 4 (TLR4) expression on the monocytes following aerobic training and resistance exercises specifically in individuals with diabetes and obesity [4].

One of the causes of COVID-19 related mortality is coagulopathy. COVID-19 leads to a cascade of pro-inflammatory cytokines, which damages the hematological system. The cytokine storm leads to an increased risk of coagulation and endothelial dysfunction. This cascade results in the enhanced probability of thrombosis in veins and arteries. Physical inactivity is one of the leading risk factors of coagulopathy, which exacerbatesa leading risk factor of coagulopathy, exacerbating the COVID-19 patients' condition [46].

Considering the protective role of physical activity against COVID-19, policymakers and governments should develop adapted action plans according to different countries' COVID-19 situation to increase physical activity during the COVID-19 pandemic [10]. Improved levels of physical activity could lead to lower COVID-19 hospitalization and the financial burden on the health system will be reduced.

LIMITATIONS

Studies evaluating the associations between physical activity and COVID-19 are limited and heterogeneous. Further high-quality studies in this domain is mandated to make more definite conclusions.

Conclusion

Engaging in regular physical activity may reduce the incidence of COVID-19 infection and severe outcomes including COVID-19 related hospitalization and death. Developing action plans to increase physical activity could be an appropriate preventive strategy.

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Informed consent statement

Not applicable

Conflict of interest statement

Authors state no conflict of interests.

Authors' contributions

FH: Conceptualization, methodology, investigation (quality assessment), revise the first draft, critical review of the final draft. BM: Design the study, investigation (data collection and extraction), critical review of the final draft. BT: Investigation (data collection and extraction), critical review of the final draft. MS: Writing original draft, Investigation (data collection and extraction), review & editing, critical review of the final draft. SSh: Formal analysis, critical review of the final draft.

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Supplementary Tables

Supplementary Table I. Joanna Briggs Institute (JBI) critical appraisal checklist for cross sectional, cohort, and case control studies.

Joanna Briggs Institute (JBI) critical appraisal checklist for cross sectional studies	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
5. Were confounding factors identified?	☐	☐	☐	☐
6. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was appropriate statistical analysis used?	☐	☐	☐	☐
Joanna Briggs Institute (JBI) critical appraisal checklist for cohort studies	**Yes**	**No**	**Unclear**	**Not applicable**
1. Were the two groups similar and recruited from the same population?	☐	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☐	☐
11. Was appropriate statistical analysis used?	☐	☐	☐	☐
Joanna Briggs Institute (JBI) critical appraisal checklist for case control studies	**Yes**	**No**	**Unclear**	**Not applicable**
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	☐	☐	☐	☐
2. Were cases and controls matched appropriately?	☐	☐	☐	☐
3. Were the same criteria used for identification of cases and controls?	☐	☐	☐	☐
4. Was exposure measured in a standard, valid and reliable way?	☐	☐	☐	☐
5. Was exposure measured in the same way for cases and controls?	☐	☐	☐	☐
6. Were confounding factors identified?	☐	☐	☐	☐
7. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	☐	☐	☐	☐
9. Was the exposure period of interest long enough to be meaningful?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐

Supplementary Table II. Results of quality assessment of the studies via Joanna Briggs Institute (JBI) critical appraisal checklist for cross sectional, cohort, case control, and case series studies.

Cross sectional studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8			
Bielik et al. (2021)	Yes	Yes	No	Yes	No	Yes	No	Yes			
Boukelia & Alataibi (2020)	No	Yes	Yes	Yes	Yes	Yes	No	Yes			
Cunningham (2021)	No	Yes	Yes	Yes	Yes	Yes	No	Yes			
de Souza et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes			
Halabchi et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Latorre-Román et al. (2021)	Yes	No	No	Yes	Yes	Yes	No	Yes			
Lee et al.(2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Li et al. (2021)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Nguyen et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Okeahalam et al. (2020)	No	Yes	U	No	Yes	Yes	Yes	Yes			
Pitanga et al. (2021)	No	No	U	No	Yes	Yes	Yes	Yes			
Rowlands et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Sallis et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes			
Tavakol et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Wang et al. (2020)	No	Yes	No	Yes	Yes	Yes	Yes	yes			
Zhang et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Cohort studies	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**
Ahmadi et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U*	Yes	U	Yes
Hamer et al. (2020)	No	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes	U	Yes
Hamrouni et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes	U	Yes
Huang et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes	U	Yes
Lobelo et al. (2021)	No	No	Yes	Yes	Yes	Yes	Yes	U	Yes	U	Yes
Marcus et al. (2021)	No	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes	U	Yes
Pinto et al. (2020)	Yes	No	Yes	Yes	Yes	Yes	Yes	U	Yes	U	Yes
Salgado-Aranda et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes	U	Yes
Case control studies	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	
Cho et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	U	Yes	
Gao et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	U	Yes	
Webber et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	U	Yes	

* U: unclear.

Can a UV-C box help the cinema industry by disinfecting video cameras?

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Summary

Introduction. *UV-C has proven to be an effective virucide and microbicide, and its cost-effectiveness allowed it to spread as a disinfecting procedure in different environments.*
Methods. *The study aims to determine the microbicide activity on Staphylococcus aureus, Escherichia coli and SARS-CoV-2 of the UV-C Boxer by Cartoni S.p.A. Three separate experiments were performed to assess the effectiveness of the UV-C disinfection device on different materials, directly on surfaces*

of a video camera and on a specific carrier for SARS-CoV-2.
Results. *In all three experiments, a significant abatement of bacterial and viral contamination was reached after 60 seconds on carriers and after 3 minutes on all examined surfaces of the video camera, with a higher reduction on glass carriers.*
Conclusions. *UV-C devices may be a valuable tool to implement in the working routine to achieve a higher level of safety in work environments.*

Introduction

In recent years, studies on the ability of microbes to colonize the environment have increased considerably, as it has been shown that surfaces can be a source of infection for humans [1]. Any inanimate object that can have infectious agents on its surface and, thus, spread them is called fomite. It has been proven how the contamination of fomites in health facilities can be a means of infection, from patients' room surfaces to healthcare workers' tools [2]. *Staphylococcus aureus*, for example, is a pathogen associated with a broad spectrum of infections both in nosocomial environments and community settings [3]. Despite it being a ubiquity that affects the skin of healthy individuals [4], it has become a relevant global health issue due to the development of antibiotic resistance. Methicillin-Resistant *S. Aureus* (MRSA) infections, in particular, are steadily growing in incidence and prevalence [4,5]. The World Health Organization (WHO) global report on Antimicrobial resistance describes how MRSA represents at least 20% of all *S. aureus* species in all WHO Regions, with some areas reporting an 80% peak [7], making MRSA a global threat and its control the main challenge for global health. Alongside Hospital-Acquired MRSA (HA-MRSA), which is an important cause of mortality in nosocomial environments [5], Community-Associated MRSA (CA-MRSA) has recently taken an essential spotlight in medical research due to its incidence among people who had no contact with healthcare environments [6]. CA-MRSA can

be transmitted by direct contact between people and between shared objects and surfaces, considering that it has proven to live in surfaces for a significant amount of days [7]. This has led to fomites being essential means of MRSA infections and outbreaks [8, 9], favoring the spread of antibiocidal resistance. Gram-negative bacteria have proven to last on surfaces and fabrics in hospital environments. *Escherichia coli*, in particular, is a very common cause of HAI [10], and there's a relevant focus on this microbe due to the recent uprising of Multi-Drug Resistant (MDR) strains with the New Delhi metallo-β-lactamase - type carbapenemases [11].
In 2020 the sudden rising of the SARS-CoV-2 pandemic urged scientists to study the virus' characteristics; among them, its' transmission means. The virus, counting more than 750 million confirmed cases and almost 7 million deaths as of 22nd of March 2023 [12], is mainly transmitted via respiratory droplets and direct contact [13]; however, it is possible for the virus to contaminate high-contact surfaces and dry surfaces in hospitals [14] stratifying the risk based on virus source, time of exposure and location of the surface. In fact, Belluco et al. proposed a classification for risk of a Sars-Cov-2 infection from surfaces based on these three factors, thus dividing the risk in "High, Medium, Low and Very Low" [15]. And while as of 5th of March 2023 the WHO declared the pandemic no longer constitutes a public health emergency of international concern [16], the need to control and study the virus has led to massive restrictions, including business shutdowns that have resulted in the loss of as many as 33 million jobs worldwide and, according to the International

Labour Organisation's report, 'The most serious crisis since World War II: Job losses are increasing rapidly worldwide' [17].

To avoid these kinds of contamination, objects and surfaces disinfection is one among all precautions needed in various settings. As seen in nosocomial environments, a good disinfection practice of stethoscope is necessary to avoid MRSA contamination, but it has been reported a lax and unreliable cleaning habit from physicians and other healthcare professionals [18, 19]. New technologies, like UV light devices, have been proven effective in disinfecting various healthcare environments and surfaces [20,21], only recently has scientific literature started exploring the potential of UV-C devices in house and work environments [22]. The correct use of UV-C technology takes the following parameters into account: distance from the light source (m), spatial light distribution, radiant power (W), irradiance (W/m^2), inversely proportional to the square of the distance, and radiation times (min). This allows more accurate disinfection of objects that are exposed to an adequate dose of UV-C, where the dose (J/m^2) is the product of the irradiation time and irradiance [23]. Simulation models, that take into account the parameters described above make it possible to estimate the disinfection capacity of systems based on UV-C technology. In particular, once the dose corresponding to a specific reduction in microbial load has been established, they enable the relative UV-C irradiation times to be evaluated for each distance, and vice versa [24]. However literature about surface contamination and control in non-healthcare environment with this type of technology is scarce and every surface in every work environment can be a fomite.

For the purpose of this study the focus is shifted to cinema industry. It was forced to halt its production by the COVID-19 pandemic, especially in the first half of 2020: movie theaters and production studies had to close for months, heavily impacting the market [25]. As described by the 2020 THEME Report [26], redacted by the Motion Picture Association, the global box office market was $12 billion in 2020, 72% lower than 2019. From the same report, it is highlighted the fact that only 46% of the U.S./Canada population went to the cinema at least once in 2020, compared to 76% of population in 2019. Video cameras, in particular, are tools that are shared among the crew and have frequent contact with different parts of the body: these factors result in video cameras being a potential route of transmission via fomite colonization. And while a protocol for the protection of workers in this work sector was developed in 2020 [27], the experiments discussed in our study might be the first experiments involving the cinema industry and disinfection of commonly shared work tools, such as video cameras.

This study aims to evaluate the microbicidal efficacy of a new UV-C device for the disinfection of cameras and cinema equipment. Equipment like this are often contaminated by hand contact and proximity to the nose, mouth, ears and conjunctivae. The performance of the device will be analyzed by placing contaminated carriers with selected microbes at sensitive spots on the camera.

Materials and methods

The experiment was conducted between December 2020 and February 2021 at the Department of Molecular and Developmental Medicine, University of Siena, Italy. The UV-C device is a "Cartoni UV-C BOXER number BX0002", provided by Cartoni S.p.A. (Fig. 1). The UV-C boxer has a large sliding box-like container for safe loading and disinfection of multiple pieces of gear at the same time. There are 10 UV-C lamps, "OSRAM PURITEC HNS UV-C", at 255 nm (0.9 Watt/each) (OSRAM GmbH, Munich, Germany) equally distributed on the top of the internal chamber. All six internal walls are reflective, to allow the UV rays to reach every surface of the device to disinfect. If the box chamber door is not safely locked, a switch sensor placed directly on the device door does not allow the UV-C lamps to be turned ON. The UV-C lights are activated by closing the box and pressing the switch button. A timer control can be used to program switching ON and OFF the device to set disinfection cycles.

Three different types of experiments were conducted. The first is a test of inactivation of selected bacterial isolates at a fixed distance, with two exposure times and different carrier materials. The second experiment consisted of a disinfection test of a video camera with contaminated carriers attached in different spots of its surface. The third experiment involved an inactivation test for the SARS-CoV-2 virus placed in a plastic cap inside a polylactic acid support with two UV-C permeable quartz walls (on the upper and bottom part).

Fig. 1. The UV-C Boxer from Cartoni S.p.A.

FIRST EXPERIMENT

In this first experiment, two different bacteria were used: *S. aureus* ATCC 43300 and *E. coli* ATCC8739. A 0.5 McFarland inoculum for each bacteria strain was prepared, and from each inoculum, several scalar dilutions were performed. Then 100 μl of each dilution was spread on a 20 cm² carrier, with a sterile spatula, and let dry inside the laminar flow hood. Three different materials were selected: metal carriers, glass carriers and plastic carriers. Carriers were then positioned horizontally in the UV box, 50 cm from the upper light sources of the device. Carriers were exposed for 30 seconds and 60 seconds to UV-C rays. Additional carriers were placed out of reach of UV-C radiation, covered with an aluminium shell outside the device (positive controls). After the treatment, exposed and non-exposed carriers were transferred to 90 mm Petri dishes and 10 mL Dey and Engley (D/E) neutralizing broth medium was added (Liofilchem S.r.l., Teramo, Italy). Subsequently, the D/E medium was transferred to a 50mL Falcon centrifuge and spun for 40 minutes at 4500 rpm. Next, the supernatant was eliminated and the pellet re-suspended in 1mL D/E medium. Finally, 100 μl was transferred to Mannitol Salt Agar Petri dish (Oxoid Limited, Hampshire, United Kingdom), for *S. aureus*, Brilliance *E. coli*/Coliform Selective Agar Petri dish (Oxoid Limited, Hampshire, United Kingdom), for *E. coli*, and incubated at 36°C for 48 h. This experiment was conducted in triplicates.

SECOND EXPERIMENT

The contaminated device used for this experiment is a Sonyh Ampex CVR (BVW) 400P video-camera (Sony, Tokyo, Japan) which was placed on the sliding container of the box. To conduct this study, it was necessary to locate selected spots on the video camera to place the test microbic sample following two criteria: 1) spots with a high frequency of contact with human skin and, thus, very likely to be contaminated in everyday use of the device; 2) spots where the UV-C light might not reach directly, to test the microbicide effectiveness of reflected light on the camera. Five spots were identified: Spot A, 23 cm from the light sources (handle position, direct to the light sources); Spot B: 30 cm from the light sources (ocular position, not direct to the light sources); Spot C: 33 cm from the light sources (lateral position, not direct to the light sources); Spot D: 34 cm from the light sources (keypad position, not direct to the light sources); Spot E: 50 cm from the light sources (shoulder pad position, opposite to the light source) (Fig. 2).

The test microorganism for this experiment was *S. aureus* ATCC 43300. On each spot, a 20 cm² plastic carrier was placed, and the *S. aureus* inoculum was spread on each carrier with a sterile spatula and left to dry inside a laminar flow hood. Positive control was also prepared with another 20 cm² plastic carrier which was left in the lab during the experiment, out of range of UV radiation. The concentration of the inoculum in the Treated Samples and Positive controls was 1.5×10^7 CFU/mL for each spot. The video camera was exposed to the

Fig. 2. The video camera and the position of the selected spots for experiment 2.
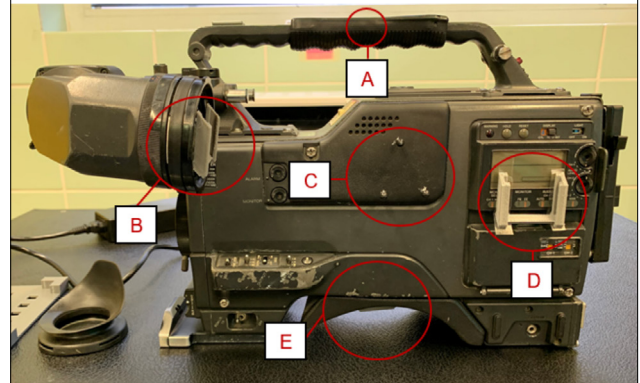
UV-C light inside the closed box for 3 minutes. After the treatment, the used protocol to prepare the samples was the same procedure used for the first experiment. This experiment was conducted in triplicates.

THIRD EXPERIMENT

In the last experiment, SARS-CoV-2 was tested (Lot: SARS-CoV-2_COV2019 ITALY/INMI1) using the VERO E6 C1008 (ATCC CRL-1586) cell line as host cell. We have designed a support made of polylactic acid (PLA) then printed it with an FDM 3D-Printer Anycubic (Shenzhen Anycubic Technology Co., Hong Kong, China). At both ends of the PLA support, two quartz carriers (UV-C permeable) were placed and between them, a plastic cap with the inoculum drop placed inside of it. The PLA support was positioned at the centre of the sliding grid of the box (Fig. 3). The Inoculum consisted of with 100 μL of viral suspension. The suspension virus used was $10^{6.88}$ TCID50%/mL (6.88 expressed by Log_{10}). The device irradiated the surface for 3 minutes. Three samples inoculated with the virus were subjected to the action of the UV-C box as per protocol. In comparison, three samples were inoculated but not treated with UV to determine viral titer after recovery and examined immediately after inoculation. The collected suspensions were inoculated into a multi-plate into which the VERO E6 cell cultures were fixed. Plates were incubated for three days at 37°C ± 2°C at 5% CO_2 in a humidified atmosphere. After the exposure time, we tested the residual virus activity by evaluating the Tissue Culture Infective Dose of 50% (TCID50%).

STATISTICAL ANALYSIS

In the database, the variables collected were the Petri dish ID, CFUs/mL, microorganism species and inoculum concentrations. Data analysis and statistical computations were performed using Microsoft Excel software (ver. 16) for preliminary statistical evaluations of empirical data and Stata software Ver 16 for the statistical analysis. The results of each experiment in triplicate were expressed as mean CFU/mL for each test for the experiments involving

Fig. 3. (a) the PLA support (grey part) used for the test. Inside the support, the viral inoculum has been placed in a plastic test tube cap (blue cap). (b) Placement of the PLA support on the metal grid of the device (view from above).
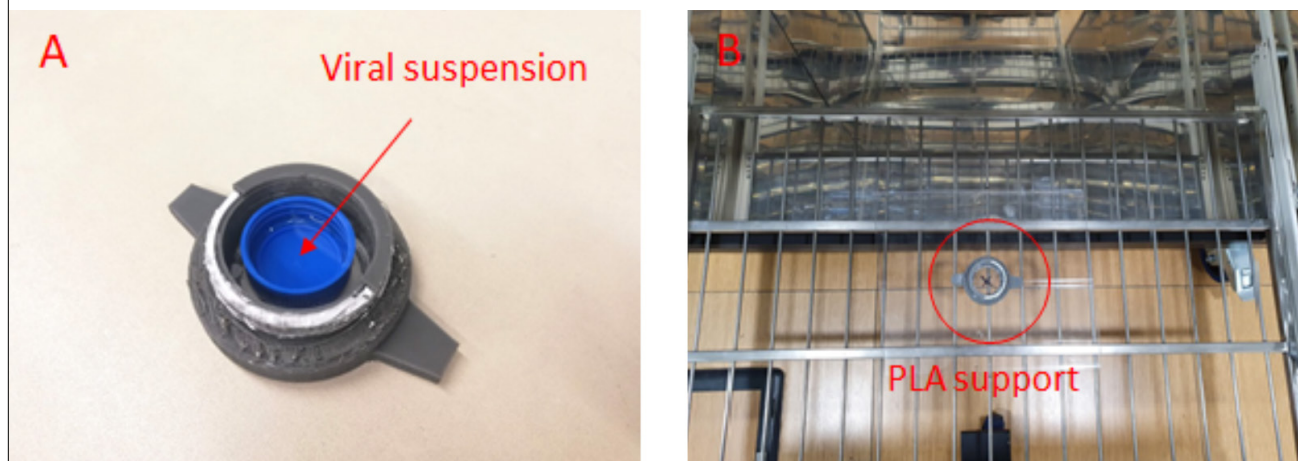
bacteria. The mean logarithmic reduction and its 95% confidence interval were calculated from the replicates data of the microorganisms and compared with positive controls.

Results

FIRST EXPERIMENT

This experiment showed that the higher bacterial inactivation effect is reached for all two strains at 60 seconds, although at 30 seconds, there is a significant reduction in the bacterial load.

With a concentration of 1.5×10^7 CFU/mL on a plastic carrier, the mean bacterial inactivation of *S. aureus* was 5.06 Log_{10} after 30 seconds of exposure to UV-C light and 5.96 Log_{10} after 60 seconds. *E. coli*, instead, on the same type of carrier and with the same concentration, was reduced to 4.56 Log_{10} after 30 seconds and 5.20 Log_{10} after 60 seconds. On a metal carrier, instead, the mean bacterial inactivation of *S. aureus* was 4.63 Log_{10} after 30 seconds and 6.72 Log_{10} after 60 seconds. *E. coli* on the same carrier was reduced to 5.14 Log_{10} after 30 seconds and complete inactivation of 7.48 Log_{10} after 60 seconds. Finally, considering glass carriers, the mean bacterial inactivation of *S. aureus* was 5.61 Log_{10} after 30 seconds and 6.96 Log_{10} after 60 seconds, while the reduction of *E. coli* was 6.13 Log_{10} after 30 seconds and complete inactivation of 7.48 Log_{10} after 60 seconds.

The lower concentration tested, 1.5×10^6 CFU/mL, showed the following results: on plastic carriers, S. *aureus*' mean bacterial inactivation was 4.96 Log_{10} after 30 seconds and 5.68 Log_{10} after 60 seconds, while the mean reduction of *E. coli* concentration on the same carrier was 4.26 Log_{10} after 30 seconds and 5.90 Log_{10} after 60 seconds. *S. aureus* was reduced on metal carriers by 5.46 Log_{10} after 30 seconds and 6.48 Log_{10} after 60 seconds, while *E. coli* was reduced by 5.28 Log_{10} after 30 seconds and 6.04 Log_{10} after 60 seconds. Finally, on glass carriers, *S. aureus* was reduced by 6.22 Log_{10} after

30 seconds and 5,88 Log_{10} after 60 seconds, while *E. coli* was inactivated entirely after 30 seconds, same value consequentially after 60 seconds.

The highest reduction was seen in glass carriers, whereas the smallest reduction was seen in plastic carriers. The complete data can be seen in Table I.

SECOND EXPERIMENT

These experiments showed that after 3 minutes of UV-C exposure of the video camera inside the Cartoni UV-C BOXER, there is a significant reduction in the bacterial load. After a 3 minutes' exposure to the UV-C light inside the box, the mean bacterial inactivation in plastic carriers on Spot A was 6.33 Log_{10}; on Spot B was 4.74 Log_{10}; on Spot C was 4.83 Log_{10}; on Spot D was 4.89 Log_{10}; finally, on Spot E was 5.00 Log_{10} (Tab. II).

The results are similar with those obtained in the first experiment, despite different exposure times. The findings also highlight the direct and indirect (from reflection) effect of UV-C light on target objects.

THIRD EXPERIMENT

The tests showed that for the carriers located on the device grids, 5.37 Log_{10} reduction (>99,999%) was reached when tested against SARS-CoV-2, with an irradiation time of 3 minutes for all the three repetitions (Tab. III).

Discussion

Cinema studies work in different environments, from open spaces to little rooms, where maintaining a safe distance can be problematic, and equipment is shared. This pandemic represented a challenge to step up technologies and techniques to keep safety in every work environment.

We conducted this test to see if devices like the Cartoni UV-C box can be a practical solution to control fomites infection in a peculiar work environment like movie

Tab. I. CFU/mL logarithmic reduction of *S. aureus* and *E. coli* on plastic, metal and glass carriers after UV-C irradiation inside the box, experiment 1.

| Bacteria | Carrier | 30 seconds exposure | | | |
| | | 1.5×10^7 (CFU/mL) | | 1.5×10^6 (CFU/mL) | |
		Mean	95% CI	Mean	95% CI
S. aureus	Plastic	5.06	4.73-5.40	4.96	4.74-5.17
	Metal	4.63	3.33-5.92	5.46	4.46-6.46
	Glass	5.61	5.51-5.70	6.22	5.71-6.73
E. coli	Plastic	4.56	3.95-5.16	4.26	3.43-5.09
	Metal	5.14	4.04-6.23	5.28	5.18-5.38
	Glass	6.13	5.87-6.39	6.48	6.48-6.48
Bacteria	Carrier	60 seconds exposure			
		1.5×10^7 (CFU/mL)		1.5×10^6 (CFU/mL)	
		Mean	95% CI	Mean	95% CI
S. aureus	Plastic	5.96	5.74-6.17	5.68	4.78-6.59
	Metal	6.72	5.25-8.20	6.48	6.48-6.48
	Glass	6.96	6.45-7.47	5.88	4.72-7.05
E. coli	Plastic	5.20	4.72-5.69	5.90	4.77-7.03
	Metal	7.48	7.48-7.48	6.04	5.19-6.89
	Glass	7.48	7.48-7.48	6.48	6.48-6.48

Tab. II. *S. aureus* ATCC 43300 CFU/mL logarithmic reduction on plastic carriers after UV-C irradiation inside the box, experiment 2.

| Spot | Log_{10} reduction after 3 minutes exposure | |
	Mean	95% CI
A	6.33	5.90-6.75
B	4.74	4.14-5.33
C	4.83	4.75-4.91
D	4,89	4.12-5.65
E	5.00	4.79-5.21

studios. We first wanted to test if there is any significant difference in the microbicide activity of the UV-C lamps between different types of surfaces. In the first experiment, the greatest reduction was observed on glass carriers, with the total abatement for *E. coli* and between 6 to 7 log_{10} (between 99.9998% and 99.99999% reduction) for *S. aureus* at one minute of exposure. In contrast, the smallest reduction was observed on plastic carriers. A possible explanation of the different abatements on the carriers may be attributable to a dissimilar hydrophobic condition of the materials that do not allow the same dispersion of the drop on the carrier. The latter may cause a superposition of microbes exposed to UV-C rays. Coughenor et al. showed how MRSA survives more on plastic and vinyl, posing as a hypothesis that they have a microscopically coarse structure, which provides more

protection from dehydration, comparing this to glass, instead, being a smooth surface and having the shortest survival time [28].

The next step was to see how the UV-C box performed on actual equipment from the carrier. As previously stated in the experiment setup, while selecting the spots, we considered not only the direct or reflected exposure to the UV light but mainly areas of high contact with different body parts. While utilizing a video camera, the operator makes direct contact or close contact with several body districts such as the eyes, hands, mouth and ears.

The microbiological results showed a significant reduction in all five spots after 3-minute irradiation inside the UV-C box. This experiment showed how the logarithmic reduction also depends on the carriers' position. Direct or reflected on the walls, the light irradiates the selected spots differently. The highest decrease was observed in spot A (handle position), with a 99.99995% reduction of bacterial load after 3 minutes of exposure, while the worst logarithmic reduction was observed in spot B (ocular position), with an abatement of 99.998%. Spot B was selected because it is in close contact with the human eye, possible contamination with tears, and proximity with the conjunctival mucosae. As previously stated, MRSA can be pathogenic when transmitted via unanimated surfaces. While MRSA

Tab. III. SARS-CoV-2 logarithmic reduction on the carrier after UV-C irradiation, experiment 3.

Repetition	Time of exposition	TCID50% untreated control (Log_{10})	TCID50% of virus after treatment (Log_{10})	TCID50% reduction (Log_{10})
1	3 min	6.86	1.5*	5.36
2	3 min	6.87	1.5*	5.37
3	3 min	6.87	1.5*	5.37

* The value of Log TCID50 = 1.5 means total viral inactivation

keratitis and post-operative endophthalmitis have been reported leading to poor visual outcomes, these kinds of infections are still very uncommon, and not only the percentage of MRSA eye diseases are quite low, but also they generally present with a mild clinical history and a good response to first-line therapy [29]. Spot C, where the box reached a 99,998% reduction, was identified as a surface in contact with the ear, while Spot D is crucial because the presence of buttons and a display there make it a high contact zone. Considering how bacteria can widely contaminate computer keyboards [34] and mobile phone surfaces [35] due to their frequent utilization. The results obtained here of abatement of 99,998% are in line with other studies performed on different settings [30, 31]. To be noticed was the interesting result obtained in spot E (shoulder pad position), with a microbe reduction of 99.999%, where the light could only irradiate the plastic carrier due to the reflective wall under the positioning grid.

We lastly tested the virucide activity on SARS-CoV-2. A mean reduction of 5.37 Log_{10} across all three repetitions of the same test was reached in a 3-minute exposure.

Regarding SARS-CoV-2, a significant number of studies showed the persistence of the virus in different types of surfaces and materials. Gonçalves et al. in 2021 showed that, while COVID-19 can be found in a wide range of surfaces with different materials and environments, the availability of pathogenic viruses on them is yet to be demonstrated, so it is not yet clear if a COVID-19 infection from fomites is possible or not [32]. Considering the obtained results, the same considerations discussed in the previous paragraphs about the different camera spots can also be done for SARS-CoV-2: the virus presence in the conjunctival sac can be a source of spread, and ocular manifestations may be part of the early symptoms of the disease, as stated in the meta analysis by Zhong et al. [33]. The same study highlighted how conjunctival swab tests for viral RNA resulted in positive in 3.9% of all patients. The study could not confirm nor exclude the possibility of a SARS-CoV-2 infection due to the eye as a potential source of disease, also considering how the percentage of positivity of swabs does widely vary in literature [34-36]. In all three experiments, the UV-C box managed to reduce the contamination in different samples in a short span. These results confirmed the efficacy of UV-C disinfection against microbes such as MRSA and SARS-CoV-2, aligning with other studies. The interest in UV-C disinfection comes from the ability to design easy-to-use devices in everyday routine and the reported resistance of some bacterial strands to common chemical disinfectant agents [37, 38].

In the film industry segment, where expensive devices are used and shared every working day, it is crucial to preserve the integrity of the materials the devices are made of. UV-C after long and repeated exposures can irreversibly damage irradiated surfaces [23]. From the tests performed, we believe that the duration of the disinfection cycle is not sufficient to alter the physical properties of the camera and the film recorded inside, even with consecutive cycles of irradiation. Also, it must

be considered how chemical disinfectants may stiffen plastic if not used appropriately and with the appropriate chemical for every machine.

Also, UV-C disinfection can represent a more environmentally friendly alternative to chemical disinfection. Although the lamps used in the Cartoni UV-C box do have mercury among their components, which represents a costly waste to dispose of, there is an increasing focus on LED UV-C lamps, which may become a solution to avoid toxic wastes and to lower the energy demands of the disinfection devices.

One of the possible limitations of this study is that there are no data regarding the energy doses on every spot on the camera, not allowing this study to make a thorough consideration on the possible values of dose/microbe abatement on every step area. While we can expect a lower value on sites where only reflected light could reach the surfaces, possibly related to the higher microbial reduction on Spot A (directly facing the UV-C lamps), identifying a technical dose/reduction value can be a point of interest for future studies. Another limitation of this study is that it does not report any information about the potential transmission of the microbes from the treated surfaces to the camera operators and vice versa, like in hand to surface contamination. Although there's plenty of evidence of persistence of the microbes in different surfaces and environments [39, 40] the evidence of transmission of SARS-CoV-2 via fomites is low [41] and needs further research. In addition, the opportunity to expand current knowledge in the field of UV disinfection, even at frequencies other than UV-C [42], could add information on the resistance mechanisms of microbes that persist for long periods on treated surfaces.

Conclusions

The microbiocidal activity of the UV-C boxer was effective on three different types of materials in a short time of exposure to UV light. Effective disinfection can be obtained with UV-C regardless of the position of the surface with direct or reflected rays. Further engineering and research applications on this technology could encourage companies and workers outside the healthcare context to use this type of device to maintain a safe working environment. In combination with complementary disinfection techniques (*e.g.* chemical disinfectants) and adherence to established best practices, the use of this innovative tool has the potential to improve the overall safety standards of working environments, in particular by effectively reducing the risk of microbial contamination of various cinema equipment and surfaces.

Funding

Data availability statement

The data presented in this study are available on request from the corresponding author.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Conflict of interest statement

Cartoni S.p.A. financed the University of Siena, with G.M. as the principal investigator. G.M. did not receive any personal funds for the research. G.M. and G.C. are the co-founders of the company egoHEALTH which received Cartoni S.p.A. funds to cover part of the investigation. The company Cartoni S.p.A had no role in the test design, data collection or analysis, decision to publish, or preparation and discussion of the test results in the manuscript.

Authors' contributions

GM, GC: conceptualization; GM: methodology; GC, SL: software; NN, IDP: validation; GC: formal analysis; DA, IDP: investigation; GM: resources; SL, DA: writing-original draft preparation; SL, DA: writing-review and editing; NN: visualization; GM: supervision, GM, GC: project administration; GM, GC: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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COVID-19

Knowledge and identity antecedents of COVID-19 vaccine status: a study of South Carolina residents

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Summary

Introduction. *Despite over three years of learning about SARS-CoV-2 and extensive work to develop vaccines, vaccination rates remain suboptimal, thereby preventing our society from reaching herd immunity.*

Purpose. *Extant literature on vaccine hesitancy led us to hypothesize that specific socio/political variables may be contributing to low vaccination rates, particularly in South Carolina.*

Methods. *By use of Qualtrics surveys, we collected data from people across all counties in South Carolina regarding vaccine status, plans to vaccinate, and a host of demographics.*

Results. *Findings revealed that those less likely to be vaccinated against COVID-19 tended to be younger, female, republican. Interestingly, COVID-19 knowledge did not appear to differ between vaccination status groups, although COVID-19 vaccine and general vaccine knowledge did differ.*

Conclusions. *Our results suggest that while understanding of COVID-19 was relatively similar across groups, targeted and tailored interventions aimed at enhancing the public's general and COVID-19-specific vaccine knowledge may aid efforts to reach herd immunity.*

Introduction

Coronavirus Disease 2019 (COVID-19), a respiratory infection caused by the SARS-CoV-2 virus, was declared a worldwide pandemic in March 2020. As of January 2023, there have been more than 1,000,000 deaths in the United States, with risk of severe disease and death increasing with age and comorbidities, including lung disease, heart disease, diabetes, and others [1]. To fight against the spread of the virus, public health and medical experts recommended precautionary measures such as masks and social distancing to prevent the spread of the virus and slow the progression of the pandemic. In December of 2020, the FDA permitted the release of an emergency vaccination release from Pfizer-BioNTech with FDA full approval on August 23, 2021 [2]. The release of the vaccine, however, was met with much criticism and skepticism with only 53.5% of all eligible South Carolinians being fully vaccinated a year after the full approval of vaccine [3]. This statistic is lower than public health experts believe is necessary to acquire herd immunity. Lower vaccination rates may result in overcrowded emergency rooms and physicians having to work longer hours than usual leading to a surge in burnout [4]. Surges of COVID-19 have led to overburdened hospitals which has been shown to cause a significant number of excess deaths. A 2021 study estimated 12,000 and 80,000 excess deaths when intensive care unit beds were at 75% and 100% capacity respectively [5]. The negative outcomes resulting from stressed hospital systems further support the need to reduce the strain on healthcare infrastructure. Improving

vaccination rates is one mechanism that can reduce disease rates and therefore hospital burden.

Given the prevalence of vaccine hesitancy, many researchers have tried to identify the reasons why there seems to be a lack of trust in the COVID-19 vaccine. One study from Travis et al. showed COVID-19 knowledge, age, trust in science, and Trump's presidency approval were predictive of vaccine hesitancy, although this study was done prior to an official vaccine release and was based on a hypothetical vaccine becoming available [6]. In regard to age specifically, another study on sociodemographic predictors for vaccine acceptance found that the age group of 5-18 years of age had the lowest vaccine rates as of June 23, 2022 [7]. Another study found that higher levels of trust in health organizations correlated with higher COVID-19 vaccine acceptance while higher levels of trust in social media correlated with lower COVID-19 vaccine acceptance [8]. Further, a study by Carpenter et al. found that only 23% of pharmacists in southern states received COVID-19 vaccine training and that pharmacy type, attitude, and training had a significant effect on the number of vaccines the pharmacy believes they could administer [9].

Similar to Carpenter et al., a study by Leigh et al. that viewed factors associated with health care workers' vaccine hesitancy found that health care workers that made less than the national median income were more likely to be hesitant of the COVID-19 vaccine [10]. Thus, those individuals that live in impoverished areas are more inclined to interact with health care workers that are more hesitant of vaccination, which could facilitate a reciprocal distrust of vaccination between health care workers and

those they serve. In addition, a study in China by Wu et al. found that individuals who had a lower lifestyle score *i.e.*, inadequate sleep, smoking, intermittent drinking, etc. were more hesitant of the COVID-19 vaccination [11]. Thus, individuals who tend to lead lower quality lives are more likely to show greater hesitancy.

One growing area of COVID-19 literature has looked at how certain knowledge factors may influence an individual's acceptance, hesitancy, or current vaccine status and/or various prevention behaviors [6]. Although links between COVID-19 knowledge and prevention practice and vaccine intentions have been established, the domain sampling of knowledge has been scattered. For example, a survey of six countries' residents measured COVID-19 knowledge with items that measured symptoms, causes, and prevention methods, but also items assessing knowledge of the number and genesis (in terms of country of origin) of new variants [12]. Despite the high number of correct responses for the symptoms and prevention methods, less than 4% knew all the new variants or the countries of origin for the new variants. Alternatively, a recent study of young Jordanian citizens' vaccine intentions investigated how COVID-19 knowledge and vaccine knowledge (general and specific) predicts vaccine intentions, however, it is unclear exactly what questions were asked to measure participants' vaccine knowledge [13]. The current study proposes to investigate the contribution of each of these three forms of knowledge (COVID-19 knowledge, COVID-19 vaccine knowledge, and general vaccine knowledge) on vaccine hesitancy, and to do so with measures that capture knowledge strictly relevant to the respective construct domains.

Despite the volume and richness of nascent COVID-19 vaccine hesitancy literature, much of the work combines relatively discrete categories into larger categories *(e.g.,* combining vaccinated with "willing" and "delaying" with "anti-vaccine").[11] Other studies combine responses such as "no opinion" or "unsure" with other options that reflect a more direct refusal to receive a vaccine [10].We believe that there could be value in distinguishing these conceptually distinct groups *(e.g.,* "undecided" versus "no, and do not plan to"). One of the primary benefits of the current study is a direct comparison of antecedents between those that are currently vaccinated with those reporting that they are planning to get vaccinated, those that refuse to get vaccinated, and those that are undecided. By maintaining the distinctions in our outcome variables, we are better able to tease apart differences between people's vaccination status and intentions. Thus, the findings of the current study may be more illuminative regarding potential interventions geared towards particular groups *(e.g.,* those that are undecided versus that refuse to get vaccinated).

The purpose of the present study is to identify the determinants of COVID-19 vaccination hesitancy in South Carolina. In particular, the present study compares the determinants of vaccination hesitancy as expressed with various levels of hesitancy, including delay, refusal, and uncertainty. With an understanding of the factors that contribute to vaccine hesitancy against COVID-19, educational and public health campaigns can be created to reach the targeted individuals to encourage COVID-19 vaccination.

Methods

Our data collection protocols and procedures were approved by the University of South Carolina's Institutional Review Board (IRB). All members that participated in the survey were provided consent in a digital form before proceeding further with the survey. To obtain a sample that is regionally proportional to that of South Carolina's population, we used Qualtrics to achieve a sample that captured every county in South Carolina. Qualtrics' proprietary procedures include the use of traditional, double opt-in research panels that source from website intercepts, referrals from members, email lists, customer loyalty portals, and social media. These methods were used to sample all of South Carolina's geographical locations, consisting of email solicitations and online recruitment. If the prospected individuals consenting to be surveyed met criteria, they would be emailed. Our criteria for participants were that they must be 18 years of age and be a South Carolina resident.

Our collection of data started in October 2021 and ran to December 2021. At the end of our data collection represented individuals that were stratified proportionately to the county's population size of South Carolina. A copy of the survey and the items used in the measures section are provided in the supplementary materials.

Measures

COVID-19 KNOWLEDGE

Participants were asked to answer a previously used 11-item test that pertained to COVID-19 knowledge: symptoms, transmission, and treatments [6]. Questions were scored with the correct answer given a 1 while incorrect answers a 0. Thus, scores ranged 0-11.

COVID-19 VACCINE KNOWLEDGE

We deployed a measure specific to COVID-19 vaccines asking participants to answer 10 questions pertaining to COVID-19 vaccines in a true or false format. The correct answer was assigned a 1 and the incorrect answer was assigned a 0. There was a score range of 0-10.

GENERAL VACCINE KNOWLEDGE

Participants responded to 7 questions in a true or false format that pertained to general vaccine knowledge, with correct answers assigned a 1 and incorrect answers assigned a 0. Scores ranged 0-7.

VACCINE INTENTIONS

Participants were asked to identify their intentions to get vaccinated against COVID-19 as yes, I have gotten the vaccine; no, but I plan to; no and I do not plan to; or no I am undecided.

POLITICAL AFFILIATION

Participants were asked to answer a question to identify their political affiliation as Democrat, Republican, and Independent.

RACE

Participants were asked to answer a question that pertained to the racial group they most identify: White, Black/African American, Asian/Pacific Islander, Hispanic/Latino, and American Indian/Native American. Answers were recorded as White = 1 and Nonwhite = 0 for analyses.

EDUCATION

Participants were asked to answer, "What is your highest level of education" and responded with: Less than Highschool, Highschool diploma, Some college, Associates degree, Bachelor's Degree, or Post-graduate degree.

Results

Descriptive statistics for our sample are shown in Table I. In order to investigate the influence of our various predictors on vaccine acceptance, we conducted multinomial logistic regression in SPSS. Specifically, the four vaccine acceptance categories were regressed on the predictors with "yes" as the reference category. Results showed our omnibus model of antecedents was predictive of vaccine hesitancy ($\chi^2(24) = 444.3$, $p < .001$, Nagelkerke $R^2 = .366$). Although the full results of this analysis are reported in Table II, we will concentrate on detailing themes that were found, particularly between "yes" and "no, and I do not plan to."

Education level and age were statistically significant predictors for all categories. Older and more educated participants were more likely to report being vaccinated than those that chose the remaining three responses ($p < .001$), although the effect sizes for age were quite small (Tab. II). Race was not found to be a statistically significant predictor of vaccine acceptance except when comparing "no, I'm undecided" to "yes." Here, white participants were 35% less likely to report "no, I'm undecided" compared to nonwhite participants (OR = .544, $p < .05$). While sex was not a statistically significant predictor of "no, but I plan to," males were less likely to report "no, and I do not plan to" and "no, I'm undecided" than females (OR = .393 and OR = .498, $p < .05$ respectively).

Political affiliation, like sex, was not a significant predictor of "no, but I plan to," but did share similar patterns of relations with the other two categories. Specifically, participants reporting a Democratic affiliation were less likely to report either "no, and I do not plan to" (OR = .342, $p < .001$) or "no, I'm undecided" (OR = .483, $p < .01$).

COVID vaccine knowledge, general vaccine knowledge, and COVID knowledge scores were not differentiated between vaccinated participants and those that reported "no, but I plan to." Of the three knowledge scores, only COVID vaccine knowledge was a significant predictor of "no, I'm undecided" where those scoring lower on the test were more likely to report indecision compared to those that responded "yes" (OR = .797, $p < .01$). The most pronounced influence of knowledge scores came when comparing participants reporting "no, and I do not plan to" to vaccinated participants. Although COVID knowledge scores did not differ meaningfully between these groups, participants with lower COVID vaccine knowledge and general vaccine knowledge were far less likely to report being vaccinated than "no, and I do not

Tab. I. Means for demographic variables by vaccine status.

	Yes (n = 1063)	No, but I plan to (n = 123)	No, and I do not plan to (n = 407)	No, I'm undecided (n = 172)
Gender (n = 1758)				
Male	347 (70%)	31 (6.3%)	86 (17.3%)	32 (6.5%)
Female	711 (56.3%)	92 (7.3%)	321 (25.4%)	138 (10.9%)
Education (n = 1765)				
Less than high school	28 (33.7%)	10 (12%)	36 (43.4%)	9 (10.8%)
High school diploma	212 (48.1%)	46 (10.4%)	120 (27.2%)	63 (14.3%)
Some college	237 (51.7%)	32 (7%)	131 (28.6%)	58 (12.7%)
Associate degree	178 (66.7%)	15 (5.6%)	58 (21.7%)	16 (6%)
Bachelor's degree	257 (77.4%)	15 (4.5%)	43 (13.0%)	17 (5.1%)
Post graduate degree	151 (82.1%)	5 (2.7%)	19 (10.3%)	9 (4.9%)
Age (n = 1763)	48.91	34.80	38.98	37.95
Race (n = 1732)				
White	812 (61.7%)	73 (5.6%)	316 (24%)	114 (8.7%)
Nonwhite	233 (55.9%)	49 (11.8%)	81 (19.4%)	54 (12.9%)
Political Affiliation (n = 1186)				
Republican	392 (58.2%)	32 (4.7%)	197 (29.2%)	53 (7.9%)
Democrat	365 (71.3)	51 (10%)	56 (10.9%)	40 (7.8%)
COVID Knowledge	9.46	8.90	8.54	9.13
COVID Vaccine Knowledge	8.61	7.96	7.09	7.85
General Vaccine Knowledge	3.20	3.02	2.33	2.83

Tab. II. Odds ratios and confidence intervals from multinomial regression

	No, and I do not plan to	No, but I plan to	No, I'm undecided
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age	.980 (.97, .99)*	.964 (.95, .98)*	.974 (.96, .99)*
Education	.747 (.66, .85)*	.640 (.53, .78)*	.711 (.60, .85)*
COVID Vaccine Knowledge	.651 (.58, .74)*	.908 (.77, 1.08)	.797 (.68, .93)*
General Vaccine Knowledge	.446 (.36, .55)*	.887 (.66, 1.20)	.841 (.63, 1.11)
COVID Knowledge	.992 (.89, 1.11)	.900 (.77, 1.05)	1.052 (.90, 1.23)
Race (White)	1.33 (.79, 2.23)	.618 (.35, 1.11)	.544 (.30, .99)*
Sex (Male)	.393 (.26, .61)*	.885 (.51, 1.54)	.498 (.28, .89)*
Political Affiliation (Democrat)	.342 (.22, .53)*	1.128 (.64, 2.00)	.483 (.28, .84)*

* p < .05. OR = odds ratio, CI = confidence intervals. Reference criterion was "Yes" for vaccine status. Reference categories for predictor variables are shown in parentheses.

plan to" (OR = .651 and OR = .446, p < .001 respectively). Figure 1 shows the averages of the knowledge-based questions for general COVID-19, general vaccine knowledge, and COVID-19 vaccine knowledge. Among all participants that chose "no, and I do not plan to" had the lowest scores for all knowledge-based questions and all participants that chose "yes" had the highest scores for the knowledge-based questions.

Figure 2 shows the reasons chosen that participants decided for choosing to get vaccinated for COVID-19. The top choices for getting vaccinated were for health and safety, with personal health and safety being the highest at ~87%. The second highest choice was for the health and safety of family at ~85%.

Figure 3 displays the most reported reasons that participants decided against getting vaccinated for COVID-19. The top reason against receiving the COVID-19 vaccine was distrust in the vaccine itself at ~53%. The second reason

Fig. 1. Knowledge score differences by vaccine status.
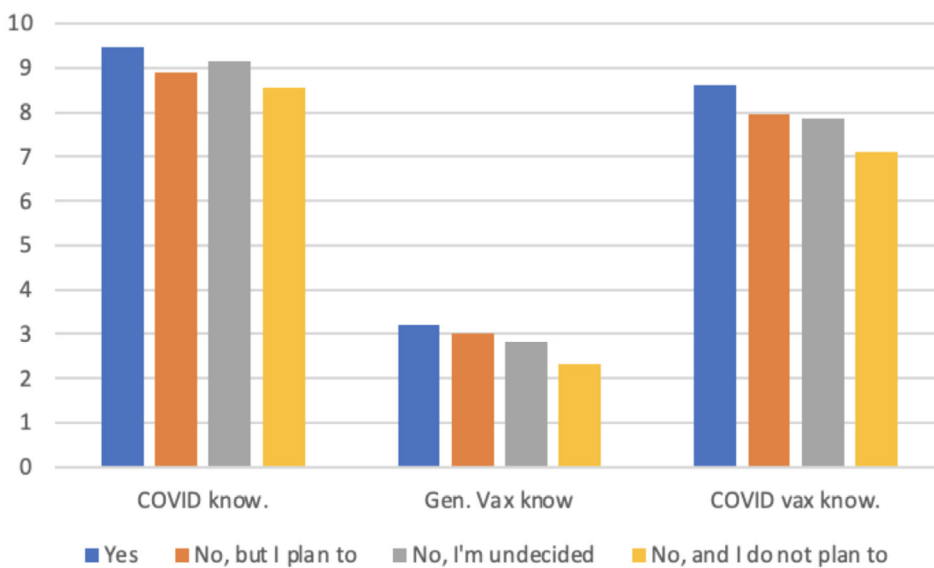
Fig. 2. Top reasons for getting vaccinated.
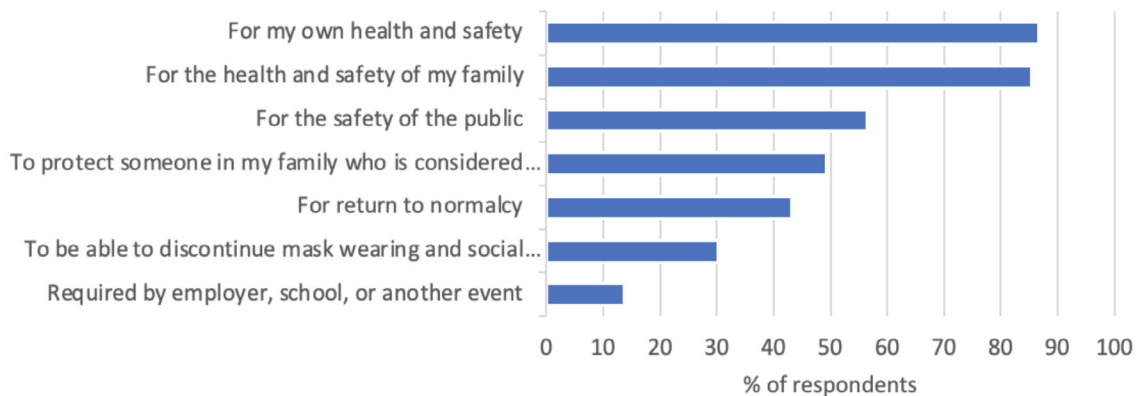
Fig. 3. Top reasons for not getting vaccinated.
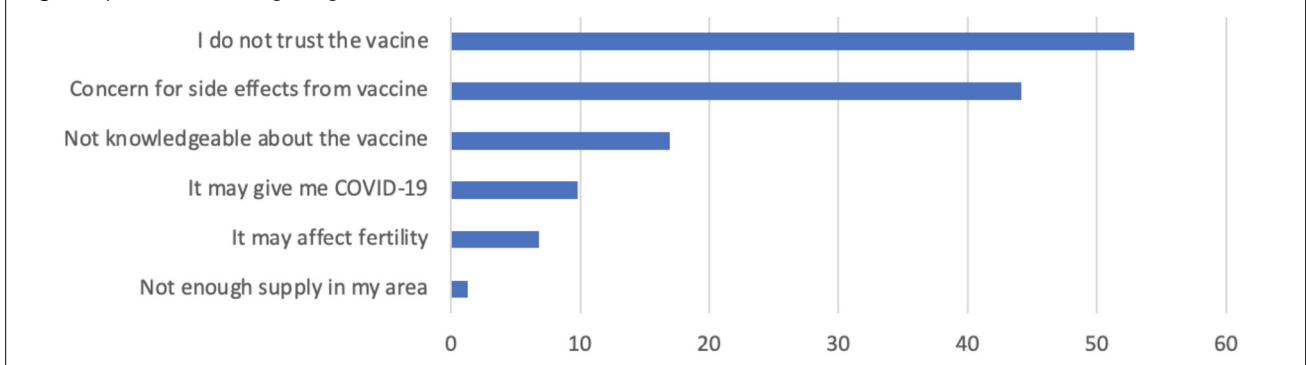
against receiving the COVID-19 vaccine is concern about the side effects of the vaccine at ~44%.

Discussion

The purpose of this study was to identify antecedents of vaccine acceptance within the South Carolina community. Administering a survey to residents of every county in South Carolina, we explored demographic, political, and knowledge-related predictors to determine the likelihood of vaccination against COVID-19. Findings revealed several factors that appear to be influential to getting vaccinated: age, sex, political affiliation, COVID-19 vaccine knowledge, and general vaccine knowledge. Our hope for this project is to use these findings to target individuals with COVID-19 vaccination education and encourage vaccination in hopes to eventually reach herd immunity against COVID-19.

According to our results, education level and age were associated with increased COVID-19 vaccine acceptance. Our research suggests that a rise in education tended to have an increase in vaccine acceptance. The relationship between education and vaccine acceptance may be manifested via an understanding of how to decern whether information is credible, an important skill learned in higher education [15]. The finding of the effect of age on vaccine acceptance may be due to older generations having more frequent contact with their doctors and physicians. According to Kini et al., older individuals are more likely to frequent medical offices due to a chronic disease that needs to be treated which allows them to be more informed on immunizations recommendations [16]. In congruence, Kini et al. suggests that younger individuals consider themselves at a lower risk for contracting diseases and are therefore less likely to receive vaccinations against diseases [16].

Our results showed that race was not a significant predictor for vaccine acceptance except for comparing "yes" and "no, I am undecided." According to our results, white participants appear to be more conclusive in their decisions about vaccinations, whereas non-white participants seemed to hold more skepticism. This may be in accordance with the historic mistreatment and abuse towards people of color, especially in the medical and research fields as other research has found much less

trust towards modern research and medical treatment when discussing how minority individuals were treated for diseases and ailments decades ago [17]. For example, a study on the impact of the Tuskegee study by Katz et al. found that 81% of African Americans had knowledge of the Tuskegee study and that that knowledge contributed to 46% of African Americans in the study to have mistrust in scientific research [17].

In our study, men were less likely to say "no, I am undecided" than women, while women were less likely to respond with "no, but I plan to." This is consistent with previous studies done that found a gap in acceptance between men and women. According to Zintel et al., women were more skeptical towards the COVID-19 vaccine [18]. According to another study by Conis E., women's skepticism towards vaccination is traced back to the 1970's and 1980's with the surgency of feminism. The women's health movement caused an examination of the scientific immunization rhetoric which led to feelings of mistrust to doctors, scientific expertise, and medical advice that culminated into how women now perceive vaccinations [19].

According to our research, Democrats were far less skeptical of the COVID-19 vaccines than Republicans as Democrats were less likely to choose "no, I am undecided" or "no, and I do not plan to" compared to "yes." This could be an artifact of Republicans tending to rely on their endorsement of misinformation about child vaccinations and more specifically the notion that childhood vaccinations cause autism [20]. Similarly, a study by Joslyn et al. found that educated Republicans were highly conflicted about vaccinations as they showed skepticism towards vaccinations though their education proved otherwise and did not align with their personal beliefs [21].

COVID-19 vaccine knowledge, general vaccine knowledge, and COVID-19 knowledge did not have a significant contribution to "no, but I plan to." This is likely due to the influx of information on general vaccination knowledge and COVID-19 over the past two years and therefore those people that have decided to get the vaccine have already received it. Perhaps most importantly, our research revealed that both COVID-19 vaccine knowledge and general vaccine knowledge were statistically significant predictors of "yes" versus "no, and I do not plan to" whereas COVID-19 knowledge was

not. Research performed in the aftermath of COVID-19's onset but preceding the approval of a vaccine has found that COVID-19 knowledge was a powerful predictor of preventative behavior but not a statistically significant predictor of vaccine intentions when included alongside variables similar to those in the present study (*e.g.,* political identity and education) [6]. As widespread public health campaigns may have enhanced the public's knowledge about the COVID-19 disease, the misinformation of COVID-19 vaccines, and perhaps a broader misunderstanding of vaccines in general, may have persisted despite these efforts. It seems from our research that the most significant contributor to becoming vaccinated against COVID-19 is the COVID-19 vaccine knowledge scores. A study by Sahil et al. found that exposure to misinformation online about the COVID-19 vaccine has determined that the United States has dropped 6.4% in intent to vaccinate [22]. It is our contention that, based on the results of extant literature and the present study, the public would be well-served to receive interventions aimed at raising more general vaccination and immunology education, as the lack of knowledge appears to be a major factor in choosing to vaccinate despite knowing the dangers of a disease like COVID-19. A few limitations of the current study bear mention. First, the sample used in our analyses was drawn from residents of South Carolina aged 18 and older. While this was our intentional strategy, our findings and conclusions should be contextualized. Indeed, important boundary conditions or contextual features may be identified by comparing our results with those of other regional samples, as well as national and international samples. Another limitation was our selection of antecedents. We chose our model a priori as COVID-19 vaccine-related research had begun to proliferate, and therefore we only included those that we felt most proximal at the time. It is certainly the case that emerging lines of research will prove progressive in offering both nuanced and empirically supported predictors of vaccine status that we did not anticipate.

Conclusions

This study used a large sample of South Carolina residents to investigate various predictors of COVID-19 vaccine acceptance. Our findings showed that many demographic and knowledge variables could meaningfully distinguish between individual's vaccine status. In addition to exploring antecedents of vaccination status, we also made careful distinctions among the groups in which we were seeking to predict – those receiving a vaccine, planning to receive a vaccine, not planning to receive vaccine, and those that were undecided. Such distinctions could be important in constructing more effective interventions to save lives and cut down on medical costs and hospital visits.
We believe that our findings may be instrumental in future studies of vaccine acceptance, particularly COVID-19 vaccines. One prospective area of potential utility is in the use of peripheral route persuasion. In brief, humans process information, and therefore can be influenced, via two routes – a logical route that requires attentional resources (central route) and an automatic route that is quick and reflexive (peripheral route) [23]. Public health interventions have tended to rely on rational, logical appeals (e.g., educating the public on the facts), yet we have observed that despite raising knowledge regarding the subject matter (COVID-19), vaccine uptake is still suboptimal. The use of peripheral route, a more automatic form of information processing, relies on positive and negative cues and their various associations; such as, an authority figure, group identity, and evoked feelings, *etc.* As the central route interventions have frequently come from groups less trusted by those they are seeking to most influence (*e.g.,* the CDC, Democratic politicians, and scientists), it is possible that these evoked negative associations from listeners. Framing messages and embedding them with cues relevant to the targeted group (*e.g.*, delivery by a young female Republican, evoking authority relevant to young female Republicans, etc.) may be a potential persuasion tool towards vaccination for those that are otherwise opposed to vaccination, based on our research. Indeed, recent research[24] has found that the public may be most influenced when both routes are leveraged, suggesting future studies may benefit from exploring which principles of influence may work best, and for which groups and under what conditions.

Acknowledgements

Conflict of interest statement

The authors report no conflicts of interest.

Acknowledgement

Authors' contributions

B.M. was responsible for study design, data analysis, and writing the manuscript. C.P. contributed to study design, data analysis and manuscript editing. G.W. was responsible for grant funding and study design and contributed in editing the manuscript. J.T. was responsible for data collection and analysis, and contributed in writing and editing the manuscript.

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COVID-19

Knowledge and training of Italian students in Healthcare Settings on COVID-19 vaccines and vaccination strategies, one year after the immunization campaign

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Keywords

Medical education • Elective training activities • HCWs • SARS-CoV-2 vaccine • Public health

Summary

Introduction. *COVID-19 vaccines represent an important opportunity for defeating the disease, as long as high vaccination acceptance rates are achieved. Healthcare workers (HCWs) have a relevant role in the promotion of immunization among the population and since students in healthcare area will be HCWs it is crucial to provide more in-depth knowledge on vaccinations. Therefore, the aim of the study is to assess the knowledge of medical and pharmaceutical area students regarding COVID-19 vaccination and the impact of a specific Elective Teaching Activity (ETA) on the increase of students' knowledge. The ETA was held one year after the immunization campaign in Italy.*
Methods. *Students' knowledge was tested with a questionnaire before and after attending the course. Descriptive statistical methods were used to analyse the results obtained. Student's t-tests for paired data were used.*

Results. *Overall, 387 students at the University of Florence attended the course and took the same test before and after the ETA on COVID-19 vaccines. Despite achieving satisfactory average scores in the pre-course test (26/32 ± 4.0), all students were able to significantly enhance their final score (+17.1%; p < 0.001), indicating that the ETA was highly effective in improving their knowledge of COVID-19 vaccination. Medical students demonstrated a better comprehension of the role of the medical specialist in public health in the COVID-19 vaccination campaign, while some uncertainties were revealed regarding the role of pharmacists.*
Conclusions. *The results of this study confirm that specific training activities on vaccination are effective for implementing the knowledge of future health professionals.*

Introduction

Vaccinating against COVID-19 represents an important opportunity to mitigate the pandemic's spread, decrease hospitalizations and ease the burden on the healthcare system [1]. The World Health Organization (WHO) considers that all people should have access to safe and effective COVID-19 vaccines as quickly as possible, starting with those at high risk of severe disease or death [2].

Implementing global and national vaccination programs, combined with non-pharmaceutical interventions, are useful tools to reduce the spread of the COVID-19 pandemic [3]. The COVID-19 vaccination campaign started on 27 December 2020 in Italy and in Europe with the launch of Vaccination Day (effective on 31 December 2020) [4].

Currently, most countries, including Italy, are continuing to administer booster doses of COVID-19 vaccines. In May 2023, 49,598,386 people have completed the primary vaccination cycle (more than 80% of the entire population) while 40,633,693 have completed the booster dose in Italy [5]. Nevertheless, there is a growing concern that vaccine hesitancy towards COVID-19 vaccination may impede the worldwide achievement of benefits derived from preventive activities in different regions [6].

The term "Vaccine Hesitancy" has been defined as the act of delaying acceptance or refusing vaccination despite the availability of vaccination services [7] and, in 2019, the WHO included vaccine hesitancy as one of the ten threats to global health of the year [8]. Given cases of fatal adverse reactions following vaccination, the scientific community must work diligently to combat vaccine hesitancy regarding COVID-19 among the general public. The success of a worldwide vaccination campaign represents a significant challenge for the scientific community in the battle against COVID-19, and thus, it is crucial to furnish scientific evidence to mitigate any doubts held by the public [9]. Additionally, it is important to note that a recent analysis of social media revealed a substantial amount of misinformation related to COVID-19 vaccines [10].

Gaining insights into the factors that can affect the willingness to refuse COVID-19 vaccination could help in developing future public health strategies designed to boost vaccination rates [11, 12].

Starting in 2020, the Italian government has launched several campaigns and messages to encourage people to get vaccinated, including television, radio, and social media advertisements. These campaigns also addressed common vaccine myths and misconceptions [13-14].

Considering what has been stated before, an appropriate knowledge of vaccinations among healthcare workers can significantly influence vaccine acceptance among their relatives, patients and, lastly, the general population as they are considered competent persons and reliable sources of information [15]. Hence, it is important to place emphasis on the education of healthcare students who will have direct contact with patients and should follow the same guidelines as healthcare professionals [16].

Therefore, the primary objective of the study was to evaluate the knowledge of medical and pharmaceutical area students regarding COVID-19 vaccines and vaccination strategies, and the impact of a specific Elective Teaching Activity (ETA) on the increase of student's knowledge on related topics, after the release of many types of COVID-19 vaccines and a booster vaccination campaign in Italy.

Materials and methods

THE ELECTIVE TEACHING ACTIVITY

An optional ETA was held at the University of Florence (Italy) on COVID-19 vaccines and vaccination strategies. The course was attended by students from the Medicine and Surgery degree courses, as well as from the pharmaceutical area. The lessons took place at the beginning of 2022 (January and February 2022) through the Webex online platform using Moodle (Modular Object-Oriented Dynamic Learning Environment), a learning management system (LMS). Moodle is an open-source platform that enables the storage and retrieval of educational materials, the creation of questionnaires and tasks, the provision of exercise support, the attendance of online lessons, and the use of collaborative work tools.

The ETA (8 hours) included lessons on different types of vaccines developed through traditional methods and the new technologies used for COVID-19 vaccines. The purpose of this course was to make students aware of the benefits of anti-COVID-19 mass vaccination implementation based on scientific evidence. Therefore, the ETA aimed at making students acquire knowledge on the efficacy and safety of COVID-19 vaccines, by examining in depth the topic of vaccine vigilance. After the ETA, the role in the Italian COVID-19 vaccination plan of both the medical specialist in public health and the pharmacist was described to the students.

TEST

To assess the impact of the ETA available on the Moodle platform, each participant was required to complete a designated test, with the same questions, before and after attending the ETA. Although participation in the course was voluntary, only individuals who completed the ETA were eligible to take the post-lecture test. The test comprised 12 multiple-choice questions on the subjects covered in the teaching activity (supplemental file). The first nine questions were the same for students of both Medical and Pharmaceutical degrees: questions 1 to 3 focused on clinical COVID-19 vaccine development, questions 4 to 6 on the national COVID-19 vaccination plan and the categories of the population to be vaccinated, and finally questions 7 to 9 addressed the issue of adverse events following immunization (AEFI) and vaccine vigilance. Questions 10 to 12 differed according to the degree course. In detail, questions 10-12 for medical students focused respectively on the role of the medical specialist in public health. On the other hand, questions 10-12 for students of the pharmaceutical area focused on the pharmacist's role in the implementation of the COVID-19 vaccination plan in Italy. The choice of inserting a few specific questions (but the same in the pre-course and post-course tests) for each degree program was aimed at assessing the student's knowledge of the role of medical specialist in public health and pharmacist in COVID-19 vaccination respectively. A score was assigned to each correct answer, for a total of 32 points (the passing grade was 18 points). A comparison between pre- and post-course test scores was performed. In addition, the change in the number of incorrect/correct answers in the pre-and post-course test was analysed for each question.

After being given a brief explanation of the survey's objective, students consented to participate in the tests by selecting the "I agree" option in the informed consent provided along with the test. The questionnaire, which was conducted online, did not require any specific health information. The only information requested was university ID number, gender, and degree course. This information was already publicly available, therefore there was no need to seek ethical approval to conduct the study.

All data were collected and managed in an aggregated format in accordance with the European Union Regulation 2016/679 and the Italian Legislative Decree 2018/101.

STATISTICAL ANALYSIS

The results obtained before and after attending the course were analysed using descriptive statistical methods. Categorical data were expressed as numbers and percentages and then compared using the Chi-square test, while continuous data were presented as mean and standard deviation (SD) and compared using the Student's t-test.

The paired Student's t-test was used to compare the total scores obtained before and after attending the ETA. A p-value of 0.05 was considered statistically significant. SPSS was used to analyse all the data (IBM SPSS Statistics 28.0.0.0).

Results

The students who took the test before the course were 411. In detail, 387 attended the ETA and have taken both the pre and post-course tests. Of these, 297 (76.7%) were enrolled in Medicine, 59 (15.2%) in Pharmacy, 28 (7.2%) in Applied Pharmaceutical Sciences- Quality Control (SFA-CQ) and 3 (0.8%) in Chemistry and Pharmaceutical Technologies (CTF).

For convenience, we have merged students from Pharmacy, SFA-CQ and CTF into one category called "pharmaceutical area" (n=90; 23.3%). Most students were females (n = 251; 64.9%) (Tab. I), attending the IV year of study (n = 106; 27.4%).

The students from the pharmaceutical area achieved an average total score of 23/32 on the pre-course test and a score of 28/32 on the post-course test (+19.2%; $p < 0.001$). On the other hand, medical students obtained an average total score of 27/32 on the pre-course test and a score of 31/32 on the post-course test (+16.5%; $p < 0.001$). The T-student tests for paired data demonstrated a statistically significant improvement in all student groups. Regardless of their degree, students demonstrated an increase in their knowledge after attending the ETA (+17.1%; $p < 0.001$) (Tab. II).

We observed a slight difference between males and females in the percentage increase of the average pre/post course test scores in the overall student population: the test score showed a variation of +17.5% (from 25.2 to 29.6) for males, while a slightly higher variation of +18% (from 25 to 29.5) was observed in females. In addition, among medical students, females improved their knowledge slightly more than males, while among pharmaceutical area students, males reached fairly higher improvement than females (Tab. III).

Subsequently, the answers were analysed by specific topics. Table IV shows the distribution of correct answers for each question. The topic with the highest percentage of correct answers was the one on the COVID-19 vaccination plan. Independently from the degree academic course, a general trend towards increasing percentages of correct answers given in post-course tests was observed (Fig. 1).

The questions for which we observed a greater reduction in the total number of incorrect answers in the post-course test were: "Question 1 - The current COVID-19 vaccines authorized by AIFA in Italy are:" (from 52.4% to 15.5%), "Q2 - Janssen vaccine contains:" (from 32.8% to 3.9%), "Question 9 - The most AEFI for the COVID-19 vaccine concerned the administration of:" (from 67.9% to 16.6%). Another question for which a reduction in wrong answers has been observed was "Question 6 - The extension of compulsory COVID-19 vaccination currently concerns:" and in particular the decrease in incorrect answers was highlighted for the option "People over 12 years of age" (from 9 % to 1.6%). As regards other questions, incorrect answers were few and without any relevant differences between pre- and post-course tests. Furthermore, questions 10 to 12 focused on the role of the public health specialist

Tab. I. Students' characteristics (*n*=387 students).

Faculty	Gender		Year of study				
	Females n (% in Row)	Males n (% in Row)	II n (% in Row)	III n (% in Row)	IV n (% in Row)	V n (% in Row)	VI n (% in Row)
Medicine n = 297	176 (59.3)	121 (40.7)	-	-	106 (35.7)	96 (32.3)	95 (32)
Pharmaceutical area n = 90	75 (83.3)	15 (16.7)	9 (10)	29 (32.2)	6 (6.7)	46 (51.1)	-
Overall	251 (64.9)	136 (35.1)	9 (2.3)	29 (7.5)	112 (29)	142 (36.7)	95 (24.5)

Tab. II. Students' scores (mean± SD) in pre- and post-course tests.

Faculty	Pre-course	Post-course	p-value*	Δ%
Medicine	27.6 ± 3.2	31.4 ± 1.6	< 0.001*	+16.45%
Pharmaceutical area	23.1 ± 4.4	27.6 ± 3.2	< 0.001*	+19.23%
Overall	26 ± 4.0	30.5 ± 2.6	< 0.001*	+17.05%

* t-student test for paired data.

Tab. III. Average total tests scores (mean±SD), in males and females.

Faculty	Average pre-course test score	p-value*	Average post-course test score	p-value*	p-value pre-/post-course*
Medicine					
Males	27 ± 4	0.5	31.3 ± 1.7	0.3	p < 0.001
Females	26.9 ± 3.1		31.4 ± 1.5		p < 0.001
Pharmaceutical area					
Males	23.3 ± 3.8	0.09	27.9 ± 3.2	0.7	p < 0.001
Females	23.1 ± 4.5		27.5 ± 3.3		p < 0.001

* t-student test for paired data.

Tab. IV. Distribution of correct answers for questions 1 to 9

Faculty	Medicine N=297		Pharmaceutical area N=90		Overall N=387	
	Pre	Post	Pre	Post	Pre	Post
Topic: "COVID-19 vaccines clinical development"						
Question 1 - The current COVID-19 vaccines authorized by AIFA in Italy are:						
mRNA, viral vector and subunit vaccines	154 (51.9)	273 (91.9)	30 (33.3)	54 (60.0)	184 (47.5)	327 (84.5)
Question 2 - Janssen vaccine contains:						
Human adenovirus type 26 as vector	204 (68.7)	290 (9.76)	54 (60.0)	81 (90)	258 (66.7)	371 (95.9)
Question 3 - The clinical development of COVID-19 vaccines:						
carried out all clinical research phases normally expected (phase I-III studies) with overlapping timelines	286 (96.3)	297 (100)	81 (90)	89 (98.9)	367 (94.8)	386 (99.7)
Topic: "COVID-19 vaccination plan"						
Question 4 - In the national strategic plan for the prevention of SARS-CoV-2 infection, the target population to be vaccinated in the first phase were:						
Healthcare workers, long-term residents (RSA) and elderly people (> 80 years)	294 (99)	297 (100)	89 (98.9)	89 (98.9)	383 (99)	386 (99.7)
Question 5 -The use of COVID-19 vaccine in pregnancy status in Italy is currently:						
Recommended	286 (96.3)	294 (76)	83 (92.2)	89 (98.9)	369 (95.3)	383 (99.7)
Question 6 - The extension of compulsory COVID-19 vaccination currently concerns:						
People over the age of 50 years	273 (91.9)	294 (99)	74 (82.2)	85 (94.4)	347 (89.7)	379 (97.9)
Topic: "COVID-19 vaccine vigilance"						
Question 7 – Most of Adverse Events Following Immunization (AEFI) reported for COVID-19 vaccines were:						
Not serious with complete recovery	285 (96)	296 (99.7)	82 (91.1)	85 (94.4)	367 (94.8)	381 (98.4)
Question 8 - The most reported AEFIs were:						
Fever, tiredness, injection site pain	288 (97)	297 (100)	86 (95.6)	88 (97.8)	374 (96.6)	385 (99.5)
Question 9 - The most AEFI for the COVID-19 vaccine concerned the administration of:						
Comirnaty	98 (33)	269 (90.6)	24 (26.7)	53 (58.9)	122 (31.5)	322 (83.2)

Pre: refers to pre-course test; Post: refers to post-course test. AIFA: Italian Medicines Agency. Correct answers: n (%).

Fig. 1. Overall distribution (%) of correct answers in pre- and post-course tests grouped by topic.

Discussion

The aim of this study was to evaluate the knowledge of medical and pharmaceutical area students regarding COVID-19 vaccines and vaccination strategies and the impact of an Elective Teaching Activity on students' knowledge. More specifically, this study mainly focused on the efficacy of non-curricular and specific academic courses on the topic of vaccinations as an innovative learning tool for health-area students. As future medical and pharmaceutical area students will become healthcare professionals who play a prominent role in administering

in the COVID-19 vaccination campaign, we observed a low number of incorrect answers in the pre-course test and almost none in the post-course test. On the other hand, for pharmaceutical area students, we highlighted a greater reduction limited to: Q11 - "Which of the following stages of COVID-19 vaccination is the pharmacist involved in?" (from 21% to 6.6%) and Q12 – "Which of the following COVID-19 vaccines is administered by the pharmacist?" (from 38.9% to 12.2%). An opposite trend was observed for "Q10 – In the COVID-19 vaccination campaign the pharmacist has played a crucial role" (Tab. V).

Tab. V. Distribution of incorrect answers given in both tests.

Incorrect answers	Overall N = 387		Medicine N = 297		Pharmaceutical area N = 90	
	Pre	Post	Pre	Post	Pre	Post
Topic: "COVID-19 vaccines clinical development						
Question 1 - The current COVID-19 vaccines authorized by AIFA in Italy are:						
mRNA vaccines and viral vector vaccines	164 (42.4)	51 (13.2)	124 (41.8)	22 (7.4)	40 (44.4)	29 (32.2)
Only mRNA vaccines	28 (7.2)	7 (1.8)	15 (5.1)	1 (0.3)	13 (14.4)	6 (6.7)
mRNA vaccines and live attenuated vaccines	11(2.8)	2 (0.5)	4 (1.3)	1 (0.3)	7 (7.8)	1 (1.1)
Question 2 - Janssen vaccine contains:						
Monkey Adenovirus type 26 as vector	47 (12.1)	10 (2.6)	36 (12.1)	4 (1.3)	11(12.2)	6 (6.7)
SARS-CoV-2 Spike protein inserted into a vector	65 (16.8)	4 (1.0)	43 (14.5)	1 (0.3)	22 (24.4)	3 (3.3)
Human Adenoviruses type 25 and 26 as vector	15 (3.9)	1 (0.3)	13 (4.4)	1 (0.3)	2 (2.2)	-
Question 3 - The clinical development of COVID-19 vaccines:						
Was based only on phase II and III studies on a limited number of volunteers for time constraints	10 (2.6)	-	7 (2.4)	-	3 (3.3)	-
Was based only on phase III studies for time constraints	2 (0.5)	-	2 (0.7)	-	-	-
Did not follow all the same clinical research phases normally expected (phase I-III studies) but a completely different clinical trial	7 (1.8)	-	2 (0.7)	-	5 (5.6)	-
Topic: "COVID-19 vaccination plan"						
Question 4 - In the national strategic plan for the prevention of SARS-CoV-2 infection, the target population to be vaccinated in the first phase was:						
People aged 60 to 75 years	4 (1.0)	1 (0.3)	3 (1.0)	-	1 (1.1)	1 (1.1)
Prisoners	-	-	-	-	-	-
Teachers and school staff	-	-	-	-	-	-
Question 5 - The use of the COVID-19 vaccine in pregnancy status, in Italy is currently:						
Mandatory	2 (0.5)	2 (0.5)	1 (0.3)	1 (0.3)	1 (1.1)	1 (1.1)
None of the other answers	10 (2.6)	2 (0.5)	6 (2.0)	2 (0.7)	4 (4.4)	-
Contraindicated	6 (1.6)	-	4 (1.3)	-	2 (2.2)	-
Question 6 - The extension of compulsory COVID-19 vaccination currently concerns:						
Pregnant women	-	2 (0.5)	-	1 (0.3)	-	1 (1.1)
People over the age of 80 years	5 (1.3)	-	3 (1.0)	-	2 (2.2)	-
People over the age of 12 years	35 (9.0)	6 (1.6)	21 (7.1)	2 (0.7)	14 (15.6)	4 (4.4)
Topic: "COVID-19 vaccine vigilance"						
Question 7 - Most of the AEFI reported for COVID-19 vaccines were:						
Fatal	1 (0.3)	-	1 (0.3)	-	-	-
Severe	7 (1.8)	3 (0.8)	5 (1.7)	1 (0.3)	2 (2.21)	2 (2.2)
Sever with full recovery	12 (3.1)	3 (0.8)	6 (2.0)	2 (2.2)	6 (6.7)	3 (3.3)
Question 8 - The most reported AEFI was:						
Central venous sinus thrombosis	8 (2.1)	1 (0.3)	5 (1.7)	-	3 (3.3)	1 (1.1)
Myocarditis	5 (1.3)	1 (0.3)	4 (1.3)	-	1 (1.1)	1 (1.1)
Bell's palsy	-	-	-	-	-	-
Question 9 - The most AEFI for the COVID-19 vaccine concerned the administration of:						
Moderna vaccine	88 (22.7)	25 (6.5)	65 (21.9)	11 (3.7)	23 (25.6)	14 (15.6)

▶

Tab. V. *Continues..*

Incorrect answers	Overall N = 387		Medicine N = 297		Pharmaceutical area N = 90	
	Pre	Post	Pre	Post	Pre	Post
Janssen vaccine	96 (24.8)	26 (6.7)	77 (25.9)	13 (4.4)	19 (21.1)	13 (14.4)
Spikevax vaccine	79 (20.4)	13 (3.4)	56 (18.9)	4 (1.3)	23 (25.6)	9 (10.0)
"The role of the medical specialist in public health in COVID-19 vaccination" (for medical students)						
Question 10 - Which, among these, is an operational line proposed by the strategic plan of the Ministry of Health to reach the target values of the vaccination campaign?						
Supply and distribution	-	-	8 (2.7)	1 (0.3)	-	-
Needs monitoring	-	-	3 (1.0)	-	-	-
Administration of vaccinations at the local level	-	-	11 (3.7)	1 (0.3)	-	-
Question 11 - What are the responsibilities of the medical specialist in public health during the vaccination session according to the organizational layout of the region of Tuscany?						
Sanitization of vaccination boxes	-	-	-	-	-	-
Recording vaccinations on the vaccination register	-	-	2 (0.7)	-	-	-
Implementation of the preparatory activities for the management of the vaccination session	-	-	21 (7.1)	4 (1.3)	-	-
Question 12 - The COVID-19 vaccination task force of the Local Health Unit (LHU) of Central Tuscany:						
Independently manages the organization of vaccination agenda	-	-	8 (2.7)	-	-	-
Refers to the Allergology and Immunology SOS to manage the operating procedures of vaccinations in a protected setting	-	-	5 (1.7)	-	-	-
is independent of the General Management of the region of Tuscany	-	-	3 (1.0)	-	-	-
"The role of the pharmacist in COVID-19 vaccination" (for pharmaceutical degrees students)						
Question 10 - In the COVID-19 vaccination campaign the pharmacist has played a crucial role:						
In community pharmacy	-	-	-	-	30 (33.3)	34 (37.8)
In hospital pharmacy	-	-	-	-	1 (1.1)	1 (1.1)
In vaccination hubs	-	-	-	-	4 (4.4)	-
Question 11 - Which of the following stages of COVID-19 vaccination is the pharmacist involved in?						
Storage and conservation in the pharmacy	-	-	-	-	2 (2.2)	2 (2.2)
Dispensing in pharmacies (to general practitioners)	-	-	-	-	4 (4.4)	1 (1.1)
Administration in the pharmacy (to patients)	-	-	-	-	13 (14.4)	3 (3.3)
Question 12 - Which of the following COVID-19 vaccines is administered by the pharmacist?						
Moderna	-	-	-	-	13 (14.4)	2 (2.2)
Janssen	-	-	-	-	15 (16.7)	3 (3.3)
Spikevax	-	-	-	-	7 (7.8)	6 (6.7)

Pre: refers to pre-course test; Post: refers to post-course test. AIFA: Italian Medicines Agency. Incorrect answers: n (%).

or producing/commercializing vaccines, it is important to provide them with comprehensive knowledge. This will be crucial in preventing the emergence of vaccine hesitancy and ensuring confidence in vaccinations in the future. However, this study did not focus on estimating vaccine hesitancy among this group of students, but rather on the efficacy of increasing their knowledge by specific educational tools on vaccinations and COVID-19 vaccines. It is relevant to highlight that this training course was performed one year after the first immunization campaign in Italy, hence the interest in assessing students' knowledge of the various COVID-19 vaccines present at the time of the course delivery.

The results obtained suggest that the basic level of knowledge of both healthcare area students on COVID-19 vaccination was very good for medical students and fair for pharmaceutical area students. This

data could be attributed to the fact that medical students were attending the last years of the medical course (from IV to VI year), while the other students were enrolled in previous academic years.

The ETA proved to be highly effective in improving the students' knowledge of COVID-19 vaccination. Despite already achieving good overall scores on the first test, all students were able to significantly increase their final score (overall +17.1%).

The questionnaire was not previously published as it was based on all the topics covered during the course. Nevertheless, these findings are comparable with the results obtained from students participating in a previous ETA on vaccines and general vaccination strategies at the same university in the first months of 2021 at the start of the COVID-19 vaccination campaign [17]. In this last case, the population of

students also included medical postgraduate students, and a different distribution in the number of medical and pharmacy students was observed. A total of 449 students participated in the previous ETA on vaccines and vaccinations, comprising 165 students (36.8%) enrolled in Pharmacy, 261 students (58.1%) in Medicine, and 23 students (5.1%) in the postgraduate school of Hygiene and Preventive Medicine. The majority of the students were females (n = 301, 67.0%) and were in their fourth or fifth year of the academic course, just as in the 2022 course. Although the questions were different from the 2022 course edition, a comparison in terms of increased knowledge was possible. Both pharmacy and medicine students showed a significant increase in their test scores between the pre- and post-course tests. A higher increase of more than +27% was observed and it was reported by both student groups (pharmacy students increased from 19.2/32 to 26.8/32 and medical students increased from 22.0/32 to 30.1/32, p < 0.001) [16]. Maybe the higher basic level of knowledge reported by the students in this last ETA could be attributed to increased attention to the specific topic of COVID-19 vaccination. This activity was offered and delivered during the fourth wave of the COVID-19 pandemic in Italy and specifically, this study was conducted one year after the beginning of the Italian COVID-19 booster mass vaccination. Indeed, the ETA was realised when about 80% of the Italian population received the second vaccine dose and 27.5% the third vaccine shot [18]. It is possible that the timing of the study could partially explain the high interest in the course and the significant improvement in knowledge demonstrated by the students in their test scores.

The ETA has also included a section dedicated to the role of the medical specialist in public health and pharmacist in the COVID-19 immunization campaign, in Italy.

The results of the current study show that, when comparing the pre- and post-course test scores, medical students demonstrated a better comprehension of the role of the medical specialist in public health in the COVID-19 vaccination campaign with very low percentages of wrong answers per question. Instead, some uncertainties were observed on the role of pharmacist in the vaccination campaign. As a matter of fact, vaccination was implemented for the first time in pharmacies in Italy during the emergency immunization campaign against SARS-CoV-2 [19]. Given the results of this study, a particular consideration should be dedicated to the training of future pharmacists, not only in the distribution and storing of vaccines, but also in the direct administration of vaccines. In the near future, the role of pharmacists in the administration phases could be extended to other vaccinations, as happens in other European countries [20]. On the other hand, pharmacists still represent a relevant source of information on immunization, thanks to their closeness to customers.

Improvement in students' knowledge obtained in the post-course test was also demonstrated by the overall decrease in the number of incorrect answers in both groups of students. Therefore, this type of ETA proves to be useful also in tackling misinformation about COVID-19.

If we consider the international context, a recent scoping review revealed that medical students who showed hesitancy to receive COVID-19 vaccines were found to have a lack of knowledge regarding the importance of vaccinations against COVID-19. Moreover, it is also important to assess vaccine reluctance at a local level to allow medical schools to develop strategies tailored to their specific needs to encourage vaccination [21].

This study has some limitations. As mentioned earlier, it is important to note that the course was not mandatory, but rather optional. This can explain why the sample size is relatively small considering the total number of students enrolled in medical and pharmacy degree programs at the University of Florence.

Secondly, the questionnaire was not validated, and questions were developed to address all the topics covered during the course. In addition, administering a pre-test may lead to heightened awareness and focus on the test material among test-takers, potentially leading to an emphasis on achieving higher scores rather than gaining a comprehensive understanding of the subject matter. Lastly, the current study design may result in an overestimation of the intervention's efficacy due to some factors such as the regression to the mean and temporal effects.

Our results suggest a certain interest in vaccination topics by healthcare area students. In recent years, similar extracurricular activities about vaccines were included in the Italian educational system with a positive response [22-23]. Furthermore, well-trained students will have a key role in promoting vaccinations and increasing public trust [24]. Finally, their role can be more effective using innovative forms of communication [25]. In the future, a thorough evaluation of the long-term effectiveness of this type of course (*e.g.*, assess whether the students can recall most information or simulate correct actions following the most up-to-date recommendations one year after the training) could be useful to decide on possible changes to the activities, or set retraining.

Conclusions

This ETA, held one year after the COVID-19 immunization campaign, was conducted to offer students in healthcare settings an insight into available COVID-19 vaccines and new technologies applied to their development, topics that are not always extensively covered in the curriculum courses. Another goal of this ETA was to inform medical and pharmaceutical area students on the current role of the medical specialist in public health and the pharmacist in the COVID-19 vaccination campaign. The findings of this study show that the offer of advanced training courses on specific levels of vaccination prevention is effective in improving the knowledge of future health professionals, who will

be the main source of information for the population. Moreover, following the training, it will be appropriate to continue education with specific courses on communication and vaccine-counselling skills.

Acknowledgments

Informed consent statement

The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical approval was waived for this study, due to the deidentified nature of the data presented.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Authors' contributions

AB, SB, AV: conceptualization. AB, SB, JS, CS: methodology. CS, JS: formal analysis. GC, NL, AV, AB, SB: investigation. AB, SB, CS: data curation. CS: writing-original draft preparation. GC, NL, AV, AB, SB, MDR, FC, JS, PB writing-review and editing. All authors have read and agreed to the published version of the manuscript.

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Sense of Coherence (SOC) of Italian healthcare workers during the COVID-19 pandemic: analysis of associated factors

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Keywords

Summary

Introduction. *The COVID-19 pandemic has posed significant challenges for healthcare workers worldwide, potentially affecting their sense of coherence (SOC) and overall well-being. This study aimed to identify factors associated with different levels of SOC among healthcare workers, exploring demographic characteristics, work-related factors, changes in relationships and social habits, and the overall well-being.*
Methods. *A cross-sectional study was conducted among 628 healthcare workers. SOC scores were assessed using a standardized questionnaire. Statistical analyses were performed to identify associations between these factors and SOC.*
Results. *Healthcare workers had a lower average SOC score (mean: 57.1) compared to the national average in Italy (mean: 60.3). Younger age and shorter length of service were associated with a higher risk of low SOC (p < 0.0001). Healthcare workers*

in the northwestern regions of Italy had an increased risk of low SOC compared to their counterparts in the northeastern regions (p = 0.0336). Adverse pandemic-related experiences and worsening social relationships were also associated with a higher risk of low SOC (p < 0.0001).
Conclusions. *This study highlights the unique challenges and stressors faced by healthcare workers during the COVID-19 pandemic and their impact on SOC. Age, length of service, geographic location, and social status were significant factors influencing SOC levels. Targeted interventions are needed to enhance SOC and well-being, particularly for younger and newly employed healthcare workers. Strategies promoting social connections, work-life balance, and psychological support services are crucial to support healthcare workers' resilience and coping abilities.*

Introduction

The global COVID-19 pandemic has had a significant impact on people's daily lives and psychophysical well-being, leading to medical, social, and economic consequences [1].

In particular, healthcare workers have been shown to experience mental health issues at a higher rate compared to the general population. Indeed, the health care sector is already characterized by psychosocial risk factors closely related to workplace organization and worker safety, such as shifts, employment rates, emergency management, staff shortages, and daily exposure to extreme distress [2, 3].

However, the COVID-19 pandemic presented unprecedented challenges for the health care system and its workers. The world was unprepared for such an outbreak, resulting in the high transmissibility of the virus, inadequate provision of personal protective equipment, limited hospital capacity, staff shortages, increased workloads, and insufficient training for emergency healthcare workers [4]. These factors, combined with the limitations imposed by the pandemic, have significantly affected people's social lives, further deteriorating global well-being [5].

Scientific evidence has indicated that the negative stress experienced by healthcare workers can have long-term consequences on their overall well-being, attention, understanding, decision-making, and ability to provide effective care [6-8]. Therefore, it is crucial to invest in interventions aimed at improving the "Sense of Coherence" (SOC) levels among healthcare workers. SOC is a resource for managing stress, involving the identification and mobilization of external and internal resources to promote health and resolve tensions [9]. Introduced by Aaron Antonovsky in the 1970s, SOC refers to "the search for health causes, that is, factors that can generate health and well-being, individual resources and processes that promote health" [9].

According to Antonovsky, individuals with a strong SOC perceive the world as meaningful, understandable, and predictable. They view stressors as challenges and activate their own resistance resources to cope with them. Conversely, individuals with a weak SOC tend to perceive stress as burdensome. SOC represents an ongoing and dynamic sense of trust in the structured and predictable nature of life's stimuli, the availability of resources to address challenges, and the meaningfulness of these challenges, thus motivating commitment and

effort [10]. Antonovsky's SOC theory sheds light on the concept of "stress-resource interaction" and explains why people can experience improved health and well-being in stressful situations [11].

Several studies have demonstrated that individuals with high levels of SOC are aware of their resources and effectively utilize them during stressful situations. Consequently, they are less susceptible to burnout and generally enjoy better health [7, 12-15]. Therefore, SOC plays a significant role in maintaining mental health under stressful conditions, and different SOC levels influence a person's psychophysical state.

Moreover, previous research has shown that SOC levels correlate with psychological distress, with individuals possessing weak SOC being at a higher risk of mental health problems compared to those with moderate or strong SOC [16, 17]. For instance, a recent study on nurses working in Intensive Care Units found that a higher SOC level was associated with better mental health [18].

To date, there is limited scientific data on the factors influencing SOC levels among healthcare workers during the COVID-19 pandemic. Existing studies mainly focus on healthcare workers involved in the diagnosis, treatment, and care of COVID-19 patients, investigating factors related to psychological distress such as depression, anxiety, insomnia, and stress [19, 20]. Additionally, investigations into the impact of social relationships on SOC levels are often conducted in routine work situations rather than emergency contexts like the current pandemic [21, 22].

Examining the factors influencing or influenced by the global spread of emerging infectious diseases and other disasters that affect SOC levels will assist health systems in targeting preventive measures and health promotion initiatives for future pandemic phases. It is crucial to enhance healthcare workers' awareness of available resources and empower them to cope effectively with stressors [11, 23].

Protecting the well-being of medical and social health workers is a fundamental aspect of the public health response to the COVID-19 pandemic and empowering them is of utmost importance.

Therefore, the primary objective of the study was to evaluate the impact of the COVID-19 pandemic on SOC levels among healthcare workers. By identifying the specific factors associated with different SOC levels, the study aimed to provide insights for interventions and support programs that can enhance SOC and promote the well-being of healthcare workers during and beyond the pandemic.

Methods

STUDY DESIGN AND DATA COLLECTION PERIOD

This cross-sectional observational study encompassed sociodemographic characteristics, work-related factors, health status, as well as changes in relationships and social habits among healthcare workers during the COVID-19 pandemic. The data collection period for this study spanned from January 18 to May 24, 2022.

STUDY POPULATION

The study was addressed to all healthcare workers enrolled in their own Order as defined by the Italian Ministry of Health (National Federation of Orders of Medical Doctors, Surgeons, and Dentists, National Federation of Italian Veterinary Orders, National Federation of Italian Pharmacy Orders, National Federation of Nursing Professions Orders, National Federation of Midwifery Profession, National Federation of Orders of Medical Imaging and Health Professions, Technical, Rehabilitation, and Prevention, National Council of Psychologists Order, National Federation of Orders of Biologists, National Federation of Orders of Chemists and Physicists, National Federation of Physiotherapist Orders).

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria for this study consisted of healthcare professionals working in all areas of the healthcare system, who were duly registered with their respective professional orders, and operated in either the public or private sector, or both. On the other hand, individuals who were not currently practicing as healthcare professionals, and who did not work in the public or private sector, or in both, were excluded from the study.

DATA COLLECTION TOOLS

The study employed a structured questionnaire, developed using Google Forms, which consisted of some validated sections. The questionnaire was disseminated through major social networks, including popular social media platforms and messaging apps. The specific names of the social networks were not disclosed due to copyright and intellectual property considerations. The questionnaire comprised four sections: (i) socio-demographic, anthropometric, and work-related information; (ii) the WHO Well-Being Questionnaire (WHO-5); (iii) social relationships; and (iv) impact on personal life satisfaction.

The impact on personal life satisfaction was assessed using the Sense of Coherence (SOC) questionnaire. This questionnaire examined individuals' awareness of their position in life in relation to their goals, expectations, standards, and concerns within the context of their culture and values.

To measure SOC, the 13-item Sense of Coherence Scale (SOC-13), developed by Antonovsky [24] and translated into Italian by Sardu et al. [25], was utilized. The national SOC mean score was 60.3 (SD: 13.6, 95% CI 59.1-61.8). The scale consisted of 13 items rated on a 7-point Likert scale (1: very often, 7: almost never, not at all), with total scores ranging from 13 to 91. Higher scores indicated a stronger SOC. The Cronbach's alpha coefficient for the SOC-13 scale in this study was 0.78. To enhance the generalizability of the study's findings and following suggestions from previous authors the SOC scores were divided into "low SOC" and "high SOC" categories [26, 27]. This categorization facilitated the comparison of variables between the two groups based on scores above and below the sample mean, respectively.

The section on socio-demographic, anthropometric, and work-related information aimed to describe and characterize the study sample. It included variables such as gender, age, marital status, country of birth, area of residence, number of people residing together, presence of minors, presence of elderly individuals, presence of disabled individuals, availability of open space at home, education, occupation, work experience, working conditions, type of employment (full-time or part-time), type of contract, occupation, and the impact of the pandemic on work.

The psychological impact questionnaire used the WHO Well-Being Questionnaire (WHO-5), which provides a simple measure of current psychological well-being [28]. A cut-off score of ≤ 50 was used accordingly to the scientific literature [29].

The section on social relationships encompassed information about family, friends, and co-worker relationships. It examined how the pandemic affected living arrangements with household members, as well as face-to-face and long-distance social relationships. It also explored visiting public places and self-care practices. Participants were asked to indicate whether their social relationships had worsened, improved, or remained unchanged since the start of the pandemic, and to what extent.

Statistical analysis

A descriptive analysis was conducted on the study population, presenting socio-demographic and occupational information, psychological well-being, and changes in social relationships categorized based on SOC levels (high/low).

The results were reported as means and standard deviations or medians and interquartile ranges for quantitative variables, and frequencies for categorical variables.

To compare qualitative and quantitative variables, the χ^2 test and Mann-Whitney U test were employed, respectively. Statistical significance was defined as a p-value < 0.05. Logistic regression models were used to calculate odds ratios and 95% confidence intervals, assessing the association between socio-demographic and occupational variables, psychological well-being, and changes in social relationships for each SOC category.

The analyses were performed using JMP PRO® software, version 14 (SAS Institute, Cary, NC, USA).

Resources

This research did not require any external resources. The questionnaires were administered through a free online platform.

Results

Overall, data were collected for 628 healthcare workers, of whom 318 (50.64%) were classified as having a weak SOC, and 310 (49.36%) were classified as having a high SOC. In this study, healthcare workers had a lower average SOC score compared to the national level in Italy (our study, average: 57.1; national study, average: 60.3) [25]. The median age of the participants included in the analysis was 38 years (interquartile range IQR 30-53), and the majority of the subjects were women (86.15%) and of Italian nationality (96.66%). The marital status was single in 46.82% of the cases. The province of residence belonged to the northeastern regions of Italy in 45.38% of the cases, northwestern in 23.57%, central in 12.74%, islands in 9.39%, and southern in 8.92%. In terms of educational attainment, the majority of the sample had a bachelor's degree (59.55%), followed by a master's degree (26.91%), a diploma (11.78%), and a Ph.D. (1.75%). The most represented job tasks were healthcare professions (86.94%), followed by medical professions (8.44%), and other professions such as psychologist, chemist, and physicist (4.62%).

The participating healthcare workers were mostly employed in the public sector, accounting for 72.45% of the sample, with a full-time contract (86.94%), and the majority had a length of service between 1-9 years (39.01%). 65.13% of the sample performed their main job in the prevention sector (55.37%). From the analysis there were no statistically significant difference by gender, birthplace, job task and SOC level (Tab. I).

Among the total respondents (n = 628), individuals aged 20-29 years showed a 6-fold higher risk (OR 5.97, 95% CI 2.66-13.45, p < 0.0001) of having a low SOC compared to those aged ≥ 60 years. Healthcare workers in other age groups showed a similar risk: specifically, individuals aged 30-39 years, 40-49 years, and 50-59 years had a three to four times higher risk of having a low SOC compared to those aged ≥ 60 years (OR 4.11, 95% CI 1.87-9.05, p = 0.0004; OR 3.01, 95% CI 1.28-7.09, p = 0.0115; OR 3.46, 95% CI 1.56-7.66, p = 0.0023, respectively).

A similar risk (OR 5.50, 95% CI 1.70-17.77, p = 0.0044) was found among individuals with a length of service of less than one year compared to healthcare workers with over 40 years of service, as well as in individuals with a length of service between 1 and 9 years (OR 5.70, 95% CI 2.07-15.70, p = 0.0008), and, to a lesser extent, in those with a length of service between 10 and 19 years (OR 3.58, 95% CI 1.26-10.13, p = 0.0164), 20-29 years (OR 3.53, 95% CI 1.21-10.33, p = 0.0211), and 30-39 years (OR 3.13, 95% CI 1.09-8.91, p = 0.033).

The northwestern regions showed an increased risk of low SOC compared to the northeastern regions (OR 1.54, 95% CI 1.03-2.30, p = 0.0336).

Being married, living with other people, having dependents under one's responsibility, and having open spaces in one's home were found to be protective factors against low SOC among healthcare workers (OR 0.54, 95% CI 0.39-0.76, p = 0.0003; OR 0.6, 95% CI 0.44-0.84, p = 0.0024; OR 0.55, 95% CI 0.39-0.78, p = 0.0009; OR 0.56, 95% CI 0.33-0.94, p = 0.0294) (Tab. I).

Based on the WHO-5 and SOC scores, female healthcare workers exhibited lower well-being and SOC scores compared to male healthcare workers (p = < 0.0006 and

Tab. I. Socio-demographic characteristics stratified by SOC level.

Socio-demographic characteristics	Low SOC ≤ 57 (n.,%)	High SOC > 57 (n.,%)	OR (95% CI)	p-Value*
Gender				
Male	37 (42.53)	50 (57.47)	Reference	
Female	281 (51.94)	260 (48.06)	1.46 (0.92-2.31)	0.1045
Age groups				
20-29	88 (61.97)	54 (38.03)	5.97 (2.66-13.44)	< 0.0001
30-39	102 (52.85)	91 (47.15)	4.11 (1.87-9.05)	0.0004
40-49	37 (45.12)	45 (54.88)	3.01 (1.28-7.09)	0.0115
50-59	82 (48.52)	87 (51.48)	3.46 (1.56-7.66)	0.0023
≥ 60	9 (21.43)	33 (78.57)	Reference	
Marital status				
Single	171 (58.16)	123 (41.84)	Reference	
Married	120 (43.01)	159 (56.99)	0.54 (0.39-0.76)	0.0003
Separated	12 (44.44)	15 (55.56)	0.57 (0.26-1.27)	0.1723
Divorced	15 (53.57)	13 (46.43)	0.83 (0.38-1.81)	0.2859
Birthplace				
Italy	306 (50.41)	301 (49.59)	Reference	
Foreign Country	12 (57.14)	9 (42.86)	1.31 (0.54-3.16)	0.5453
Region of residence				
Northeast	131 (45.96)	154 (54.24)	Reference	
Central	43 (53.75)	37 (46.25)	1.36 (0.83-2.24)	0.2189
Northwest	84 (56.76)	64 (43.24)	1.54 (1.03-2.30)	0.0336
Islands	29 (49.15)	30 (50.85)	1.14 (0.65-1.99)	0.6551
South	31 (55.36)	25 (44.64)	1.46 (0.82-2.59)	0.1998
Number of co-habitants in the same household				
1-2	161 (56.49)	124 (43.51)	Reference	
3-4	134 (43.93)	171 (56.07)	0.6 (0.44-0.84)	0.0024
≥5	23 (60.53)	15 (39.47)	1.18 (0.59-2.36)	0.6373
Minors under own responsibility				
Yes	75 (40.32)	111 (59.68)	0.55 (0.39-0.78)	0.0009
No	243 (54.98)	199 (45.02)	Reference	
Elderly under own responsibility				
Yes	67 (53.60)	58 (46.40)	1.16 (0.78-1.72)	0.4593
No	251 (49.90)	252 (50.10)	Reference	
Persons with disabilities under own responsibility				
Yes	30 (49.18)	31 (50.82)	0.94 (0.55-1.59)	0.8108
No	288 (50.79)	279 (49.21)	Reference	
Presence of open spaces in the home				
Yes	190 (48.72)	200 (51.28)	0.56 (0.33-0.94)	0.0294
No	128 (53.78)	110 (46.22)	Reference	
Educational Attainment				
Bachelor's degree	201 (53.74)	173 (46.26)	Reference	
Master's degree	77 (45.56)	92 (54.44)	0.72 (0.50-1.04)	0.0779
High School Diploma	35 (47.30)	39 (52.70)	0.77 (0.47-1.27)	0.311
PhD	5 (45.45)	6 (54.55)	0.72 (0.22-2.39)	0.5885
Job tasks				
Medical professions	29 (54.72)	24 (45.28)	Reference	
Healthcare professions	278 (50.92)	268 (49.08)	0.86 (0.49-1.51)	0.5974
Other professions**	11 (37.93)	18 (62.07)	0.51 (0.20-1.28)	0.1773
Years of service				
Less than a year	22 (57.89)	16 (42.11)	5.5 (1.70-17.77)	0.0044
1-9	144 (58.78)	101 (41.22)	5.70 (2.07-15.70)	0.0008
10-19	59 (47.20)	66 (52.80)	3.58 (1.26-10.13)	0.0164
20-29	38 (46.91)	43 (53.09)	3.53 (1.21-10.33)	0.0211
30-39	50 (43.86)	64 (56.14)	3.13 (1.09-8.91)	0.033
≥ 40	5 (20.00)	20 (80.00)	Reference	

▶

Tab. I. *continues.*

Socio-demographic characteristics	Low SOC ≤ 57 (n.,%)	High SOC > 57 (n.,%)	OR (95% CI)	p-Value*
Work setting				
Public	224 (49.23)	231 (50.77)	0.80 (0.55-1.18)	0.2582
Private	75 (54.74)	62 (45.26)	Reference	
Non-profit or third sector	19 (52.78)	17 (47.22)	0.92 (0.44-1.93)	0.8331
Work status				
Full-time	278 (50.92)	268 (49.08)	1.09 (0.68-1.73)	0.7184
Part-time	40 (48.78)	42 (51.22)	Reference	
Type of contract				
Employee contract	264 (50.32)	247 (49.68)	Reference	
Freelance	40 (64.58)	50 (35.42)	0.75 (0.48-1.17)	0.2075
Other***	14 (50.00)	13 (50.00)	1.01 (0.46-2.19)	0.9848
Work sector				
Hospital	119 (54.34)	100 (45.66)	1.26 (0.90-1.75)	0.1749
Territory	199 (48.66)	210 (51.34)	Reference	
Commuter				
Yes	82 (54.34)	68 (45.33)	1.24 (0.86-1.79)	0.2583
No	236 (49.37)	242 (50.63)	Reference	

* Chi-square test. **Psychologist; Chemist; Physicist. *** Work without a contract (verbal agreement); coordinated and continuous collaboration agreement; intermittent or on-call work; contract for work performance, professional consultancy; autonomous and occasional collaboration contract; temporary employment contract; apprenticeship contract

Tab. II. Well-being status (WHO-5 questionnaire) and SOC stratified by gender and job task.

	WHO-5	p-Value	SOC	p-Value
Mean, standard deviation (SD)	46.69 (21.49)	-	57.11 (11.21)	-
Gender				
Male	54.02 (19.47)	Reference	59.65 (11.30)	Reference
Female	45.52 (21.59)	0.0006*	56.71 (11.15)	0.0228*
Job tasks				
Medical professions	46.26 (22.33)	0.2159**	57.34 (13.13)	0.3173**
Healthcare professions	46.43 (24.45)	0.1447**	56.95 (11.02)	0.1629**
Other professions***	52.41 (20.71)	Reference	59.93 (11.09)	Reference

* T-test; ** Anova test; ***Psychologist; Chemist; Physicist.

p = 0.0228, respectively). Furthermore, there were no statistically significant differences between job tasks and well-being status and SOC (Tab. II).

Based on the WHO-5 score, 79.87% of the 318 healthcare workers with low SOC exhibited poor well-being, with a risk 7.8 times higher compared to the rest of the sample (OR 7.86, 95% CI 5.48-11.29, p = < 0.0001) (Tab. III).

Subjects whose relationships with family, friends, and colleagues worsened due to the pandemic showed a risk of approximately 2 times higher of having a low SOC, respectively (OR 2.62, 95% CI 1.81-3.79, p < 0.0001; OR 2.13, 95% CI 1.45-3.12, p = 0.0001; OR 2.11, 95% CI 1.47-3.05, p < 0.0001).

Furthermore, a statistically significant difference was found between the two SOC subgroups regarding the perception of danger regarding their work for themselves and their cohabitants. In particular, healthcare workers with low SOC had a higher perception that their work was a source of danger for themselves and their cohabitants compared to the subgroup with high SOC (p = 0.0214).

Healthcare workers who reported rarely or never visiting public places following the pandemic had a 2 times higher risk of having a low SOC (OR 2.30, 95% CI 1.33-3.99, p = 0.0030).

Additionally, taking care of oneself rarely or never compared to before the pandemic was found to be an

Tab. III. Well-being status (WHO-5 questionnaire) stratified by SOC level.

WHO-5 questionnaire	Poor well-being (≤ 50)	High well-being (> 50)	OR (95% CI)	p-Value *
Low SOC ≤ 57	254 (79.87)	64 (20.13)	7.86 (5.48-11.29)	< 0.0001
High SOC > 57	104 (33.55)	206 (66.45)	Reference	

* Chi-square test

Tab. IV. Changes in relationships and social habits following the pandemic, divided by SOC level.

Relationships and social habits	Low SOC≤ 57 (n.,%)	High SOC > 57 (n.,%)	OR (95% CI)	p-Value
How has your relationship with family changed?				
It has worsened a little/moderately/greatly	141 (66.51)	71 (33.49)	2.62 (1.81-3.79)	< 0.0001*
It has improved a little/moderately/greatly	52 (41.27)	74 (58.73)	0.93 (0.61-1.42)	0.7282*
It has remained the same	125 (43.10)	165 (56.90)	Reference	
How has your relationship with friends changed?				
It has worsened a little/moderately/greatly	245 (56.45)	189 (43.55)	2.13 (1.45-3.12)	0.0001*
It has improved a little/moderately/greatly	17 (36.96)	29 (63.04)	0.96 (0.48-1.91)	0.9142*
It has remained the same	56 (37.84)	92 (62.16)	Reference	
How has your relationship with work colleagues changed?				
It has worsened a little/moderately/greatly	157 (61.33)	99 (38.67)	2.11 (1.47-3.05)	< 0.0001*
It has improved a little/moderately/greatly	65 (43.92)	83 (56.08)	1.04 (0.69-1.59)	0.8397
It has remained the same	96 (42.86)	128 (57.14)	Reference	
Do you believe that, during the pandemic, your work has put you and the people you live with in a dangerous situation? (median, IQR)	5 (4-6)	5 (3-6)	-	0.0214**
Since the beginning of the pandemic, have you had to change your place of residence out of fear of infecting those around you?				
Yes	55 (56.70)	42 (43.30)	1.33 (0.86-2.06)	0.1948*
No	263 (49.53)	268 (50.47)	Reference	
Since the beginning of the pandemic, how often do you visit public places (restaurants, shopping malls, clubs, etc.)?				
Very rarely or never/rarely/very rarely	288 (53.53)	250 (46.47)	2.30 (1.33-3.99)	0.0030*
Quite often/very often/very frequently	9 (33.33)	18 (66.67)	1 (0.38-2.60)	1.0000*
The same as before	21 (33.33)	42 (66.67)	Reference	
Since the beginning of the pandemic, has the opportunity to see friends and relatives been reduced?				
Very rarely or never/rarely/very rarely	59 (47.20)	66 (52.80)	1.34 (0.51-3.51)	0.5497*
Quite often/very often/very frequently	251 (51.97)	232 (48.03)	1.62 (0.65-4.04)	0.2982*
The same as before	8 (40.00)	12 (60.00)	Reference	
Since the beginning of the pandemic, have you reduced direct "face-to-face" contact with family, friends, neighbors, etc.?				
Very rarely or never/rarely/very rarely	56 (44.44)	70 (55.56)	1.35 (0.63-2.93)	0.4409*
Quite often/very often/very frequently	249 (53.32)	218 (46.68)	1.93 (0.95-3.93)	0.0686*
The same as before	13 (37.14)	22 (62.86)	Reference	
Since the beginning of the pandemic, have you had time to take care of yourself?				
Very rarely or never/rarely/very rarely	240 (58.54)	170 (41.46)	3.19 (2.04-5.01)	< 0.0001*
Quite often/very often/very frequently	44 (41.12)	63 (58.88)	1.58 (0.91-2.76)	0.1072
The same as before	34 (30.63)	77 (69.37)	Reference	
Since the beginning of the pandemic, have you increased social contacts with friends and family through social networks?	4 (3-5)	4 (3-5)	-	0.3963**
Since the beginning of the pandemic, have you reduced physical contact with people who do not live with you?	6 (4-2)	5 (4-6)	-	0.0748**

* Chi-square test. ** Mann Whitney test.

additional risk factor for low SOC (OR 3.19, 95% CI 2.04-5.01, p < 0.0001) (Tab. IV).

Discussion

The COVID-19 pandemic has been a significant challenge for healthcare workers worldwide, with social and psychological repercussions. The study results have allowed us to identify some factors that influence and are influenced by different levels of SOC among healthcare workers. In this study, healthcare workers had a lower average SOC score compared to the national average in Italy (our study, mean: 57.1; national study, mean: 60.3) [25]. This suggests that healthcare workers face unique challenges and stressors in their work environment that may impact their ability to perceive and manage stress effectively and thus tend to have a weaker SOC compared to the general population or it may suggest that the SOC of this population has weakened during the COVID-19 pandemic [27].

One notable finding was the association between age and SOC. Younger healthcare workers exhibited a significantly higher risk of having a low SOC compared to their older counterparts. This finding may be attributed to various factors, such as less professional experience,

lower job security, and limited coping mechanisms developed over time. It is crucial to recognize this vulnerability among younger healthcare workers and implement targeted interventions to enhance their SOC and overall well-being.

Another significant factor associated with low SOC was the length of service. Healthcare workers with shorter lengths of service demonstrated a higher risk of having a weak SOC. This finding suggests that the experience and tenure of healthcare workers may play a crucial role in building resilience and a strong SOC. It is important for organizations to provide support and resources to newly employed healthcare workers to help them navigate the challenges and stressors inherent in their roles.

This data can be explained by the numerous new hires made in emergency situations to cope with the pandemic, which did not provide adequate support and assistance during the initial training period for newly hired workers. Some studies have shown that people with less work experience, often younger individuals, exhibited worse results in terms of mental health, resilience, and social support, likely due to anxiety arising from the perception of unfamiliarity and uncontrollability of the associated risks [30-32]. High levels of education and professional experience, resilience, and social support are necessary for healthcare professionals involved in public health emergencies.

Geographic location was also found to be a contributing factor to SOC among healthcare workers. The study revealed that healthcare workers in the northwestern regions of Italy had an increased risk of having a low SOC compared to their counterparts in the northeastern regions. Consistent with previous literature studies, frontline work in an epicenter region of the epidemic is associated with high levels of depression, anxiety, insomnia, and distress, exposing healthcare workers to the risk of developing mental health problems [31, 33].

The study identified several protective factors associated with a higher SOC among healthcare workers. Being married, living with other people, having dependents, and having open spaces in one's home were found to be protective against low SOC. These factors may provide social support, stability, and a sense of belonging, which can buffer the impact of stressors on healthcare workers' well-being. Organizations can consider implementing initiatives that promote social connections and work-life balance to support healthcare workers in cultivating a strong SOC.

The study revealed that female healthcare workers scored lower in well-being and SOC than male counterparts. Surprisingly, job tasks did not significantly impact well-being or SOC, indicating that the observed gender differences were not directly tied to work responsibilities. These findings underscored the importance of addressing gender-specific stressors and promoting support for female healthcare workers to improve their overall well-being and coping mechanisms in the profession.

Importantly, healthcare workers with low SOC demonstrated a significantly higher risk of poor well-being. This finding highlights the interplay between SOC and overall mental health.

These results are consistent with other studies that have reported that individuals with weak SOC had a higher risk of mental health problems, both during and before the pandemic [23, 34, 35]. It is believed that individuals with a stronger SOC perceive less stress associated with daily life [36] and that SOC can moderate stress factors [37, 38]. During the COVID-19 pandemic, which introduced significant stress factors in both daily life and healthcare workplaces, healthcare workers with weak SOC should pay particular attention to their mental health. Strengthening healthcare workers' SOC can potentially improve their overall well-being and resilience, enabling them to cope more effectively with the demands of their profession.

Pandemic-related factors also played a role in healthcare workers' SOC. Worsening relationships with family, friends, and colleagues due to the pandemic were associated with a higher risk of low SOC.

In fact, a higher risk of low SOC was found in individuals whose social relationships had worsened compared to those whose social relationships remained the same or improved.

The unprecedented challenges posed by the pandemic, including increased workloads, fear of infection, and social isolation, likely contributed to the strain on healthcare workers' SOC.

Consistent with previously published studies, our results emphasize a worsening of SOC in subjects with low social support. In particular, living alone, lack of social interaction with relatives and friends, and weak social ties were the main motivations for the detrimental effects of low social support on SOC [39].

Therefore, social support is a protective factor for the psychological well-being of healthcare workers during the pandemic. Social support is a psychosocial coping resource that can attenuate the negative effects of stress [39] and positively influence individuals' emotional health [40, 41], especially during periods of social distancing. Social support also leads to reciprocal benefits for members of social groups, helping them cope with daily challenges and contributing to the maintenance of their physical and psychological health [42, 43]. Organizations and policymakers should recognize the impact of these factors and implement strategies to provide support, foster social connections, and promote work-life balance during challenging times.

On the other hand, being married, living with others, having fewer dependents, having open spaces in one's home, and taking care of oneself equally or better than before the pandemic were protective factors against low SOC among healthcare workers.

The results of this study suggest the need to plan and provide timely psychological support services for healthcare workers, such as psychosocial support and support groups, to strengthen SOC and improve social support. Additionally, targeted interventions focusing on coping strategies, with multidisciplinary interventions to support healthcare personnel, are of fundamental importance.

Dedicated psychological counseling can help healthcare personnel stimulate, maintain, and improve positive emotions and free themselves from negative emotions and stress, thereby increasing behavioral flexibility, building personal resources, and eliminating the physiological effects of negative emotions [43].

Interventions aimed at promoting mental well-being in healthcare workers exposed to COVID-19 should be immediately implemented, with particular attention to newly hired workers without experience in public health emergencies and healthcare workers on the front lines in high-risk areas.

Some authors have suggested actions to mitigate the impacts of the pandemic on the mental health of professionals, protecting and promoting their psychological well-being during and after the epidemic, including remote psychotherapy [44, 45].

For team leaders or managers in healthcare facilities, it is essential to protect all staff from chronic stress and poor mental health, ensure quality communication, and ensure that staff are aware of where and how they can access mental health and psychosocial support services [46].

This study has some limitations that should be considered during the data interpretation phase. For example, the results can provide data on the association between changes in social relationships and the mental health of healthcare workers divided by SOC level, but these results cannot be exclusively attributed to the impact of the pandemic; the causal relationship cannot be determined. The study utilized a cross-sectional design, limiting causal interpretations of the associations observed. Future longitudinal studies could provide a better understanding of how SOC evolves over time in healthcare workers. Furthermore, the study focused on healthcare workers in Italy, limiting the generalizability of the findings to other contexts. Further research involving diverse healthcare settings and populations is necessary to validate and extend these findings.

Furthermore, it was considered that conducting research through electronic means risks excluding people who do not have internet access, an email account, access to a computer, tablet, or other devices, or who are not familiar with digital technologies. However, given the restrictions imposed due to this pandemic (social isolation, population quarantine, etc.), it was impossible to conduct in-person assessments. Although the survey mode may be considered a potential limitation of the study, it is estimated that in the target population of the research (working-age individuals), the total number of people excluded for this reason represents a very low percentage of potential participants.

Another limitation of the study is that the management of pathological pre-existing conditions was not explicitly addressed as an objective or a factor in the analysis. This could have implications for the interpretation of the study findings, as pre-existing conditions could potentially confound or modify the relationships between the variables studied. Future research should consider incorporating measures or adjustments to account for the influence of

pathological pre-existing conditions on the outcomes of interest. Addressing this limitation would provide a more comprehensive understanding of the factors influencing SOC and well-being in healthcare workers.

Furthermore, the questions reported in the section on social relationships focused on participants' perceptions of how their social relationships were affected by the pandemic, including whether they worsened, improved, or remained unchanged, as well as the extent of these changes. While this provides insights into participants' subjective experiences, it is important to consider potential limitations in the validity of self-reported measures. To assess the validity of this section of the questionnaire, it would be beneficial to consider conducting additional analyses to evaluate the psychometric properties of the items used. This could include examining the internal consistency, test-retest reliability, and construct validity of the social relationships section. Additionally, comparing the findings with established measures of social relationships or conducting qualitative interviews to gather more in-depth insights could help further validate the questionnaire's content.

Another limitation is that we were not able to estimate the non-response rate and the potential differences between respondents and non-respondents. This highlights the need for caution when generalizing the findings and suggests areas for further research to address this limitation.

On the other hand, this study has provided valuable insights into the Sense of Coherence (SOC) among healthcare workers and identified various factors associated with SOC levels.

However, it is important to interpret the results cautiously and avoid making causal claims based solely on the associations found. The identified associations provide valuable insights into the relationships between different factors and SOC levels among healthcare workers. However, further longitudinal or experimental studies are necessary to establish the direction of these relationships and determine if there is a cause-and-effect relationship.

Thus, it is essential to emphasize the observational nature of the study design and the need for future research to confirm and expand upon these findings.

The strengths of the study lie in its robust sample size, diverse participant characteristics, comprehensive analysis, and potential implications for interventions.

One of the key strengths of this study is the inclusion of a substantial sample size of 628 healthcare workers. A larger sample size enhances the generalizability of the findings and provides greater statistical power to detect significant associations. The diverse composition of the sample, including participants from different age groups, educational backgrounds, and professional roles, further strengthens the study's representativeness and allows for a comprehensive understanding of SOC among healthcare workers.

To note, in the context of SOC and well-being in healthcare workers, common intrinsic confounding factors to consider may include socioeconomic status, work-related factors, and personal resilience. Socioeconomic status, such as income, education level, and employment

status, can influence both SOC and well-being. Work-related factors, including job demands, satisfaction, and support, can also impact SOC and well-being. Personal resilience, coping styles, and personality traits may interact with stressors and affect SOC and well-being. To manage confounding factors, researchers employ study design strategies like randomization, matching, or stratification [47, 48].

Comparing the SOC of healthcare workers in this study to the national average in Italy adds an important dimension to the findings. This national comparison provides valuable context and highlights the unique challenges faced by healthcare professionals in their work environment. The lower average SOC score among healthcare workers in this study compared to the national average indicates that healthcare workers experience specific stressors and demands that may affect their ability to perceive and manage stress effectively.

The multifaceted analysis conducted in this study contributes to a nuanced understanding of the factors associated with SOC among healthcare workers. The examination of various factors, including age, length of service, geographic region, marital status, living arrangements, and pandemic-related experiences, allows for a comprehensive exploration of the complex interplay between these factors and SOC. By considering multiple factors simultaneously, this study provides a more holistic understanding of the determinants of SOC among healthcare workers.

The findings of this study have important implications for interventions and support programs aimed at enhancing SOC and promoting the well-being of healthcare workers. The identification of risk factors, such as younger age, shorter length of service, and adverse pandemic-related experiences, provides valuable insights for targeted interventions. Additionally, the identification of protective factors, such as being married, living with others, and having open spaces at home, can inform strategies to foster a supportive environment for healthcare workers.

In conclusion, this study contributes to the growing body of literature on SOC among healthcare workers. The results of this study can provide useful information for designing and promoting healthy and safe work environments through an empowerment program for healthcare workers, facilitating better emotional management and changes in habits and relationships caused by increased social fragmentation and self-protective behaviors, as well as better management of the long-term risk of psychological disorders among healthcare workers.

Specific support programs dedicated to healthcare workers can be planned by promoting information and training interventions on the latest prevention and coping strategies, creating supportive materials through periodic webinars to update on the latest available evidence on COVID-19.

The use of digital devices can be encouraged and implemented to provide support and promote psychological well-being through counseling activities (telephone-based and internet-based counseling services and platforms), with the aim of strengthening one's SOC and consequently improving well-being and quality of life.

In this context, a multidisciplinary approach appears crucial for proper management of the consequences on public health during the pandemic, by studying the biological effects and changes in behavioral and social habits.

Conclusions

The study findings demonstrate that younger healthcare workers, specifically those hired for less than a year, have experienced a greater impact during the pandemic. This can be attributed to the surge in emergency hires, which resulted in inadequate support and training for these individuals. Additionally, the decline or absence of family and social relationships since the onset of the pandemic contributes to lower levels of Sense of Coherence (SOC) and has significant implications for well-being. These outcomes hold particular relevance within the healthcare field, which has endured substantial pandemic-related challenges and faces potential long-term effects on the psychological and physical health of individuals and the practice of the profession. These findings lay the groundwork for further investigation and guide future prevention and health promotion interventions tailored to newly hired personnel. By addressing these issues, healthcare organizations can bolster well-being and SOC, fostering resilience among their workforce.

Ethical aspects

After providing comprehensive information about the nature and purposes of the study, participants were informed that their participation was voluntary, their responses were anonymous, and they could withdraw from the study at any time without providing any justification. It was also explained that any information collected during the study would be treated as strictly confidential and would be handled in aggregated form only by the healthcare personnel involved in the study in an entirely anonymous manner and solely for the purposes of scientific research or presentation at scientific conferences. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Acknowledgments

Conflict of interest statement

The authors declare no conflicts of interest.

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Authors' contributions

MFP, CR: Conceptualization. MFP, LM, CR: Methodology. MFP, LM, CR: Validation. MFP: Formal analysis. MFP, LM: Data curation. MFP, LM, DA, GB, AV, FS, MM, and CR: Writing-original draft preparation. MFP, LM, DA, GB, AV, FS, MM, and CR: Writing-review and editing. CR: Supervision. All authors have read and agreed to the published version of the manuscript.

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HEALTH PROMOTION

Factors influencing the first thousand days of life. The importance of Nurturing Care

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Keywords

Nurturing care • Social support • Maternity and Child health

Summary

Background. *WHO, Unicef, the World Bank and the Maternal and Child Health Partnership wrote the document "Nurturing care for early child development: a global framework action". This paper highlights the benefits of early intervention and thus the need to invest more in health during this period. The aim of our study is to assess how much social support received by pregnant mothers can influence maternity outcomes.*
Materials and Methods. *The retrospective observational study was conducted on a sample of mothers enrolled via social networks, who were administered a questionnaire from 1 July to 1 September 2021. The questionnaire consisted of 37 questions, 6 of which were used to calculate the "Maternity Social Support Scale". The ODDs Ratio was calculated.*
Results. *Our sample consisted of 3447 women. 59.01% were between 26 and 35 years of age. The mean Maternity Social Support Scale (MSSS) score was calculated to be 23.9 points.*

A low MSSS score correlated with a higher probability of stopping breastfeeding before 6 months of age (OR: 1.2; CI:1.1-1.4) and of having a caesarean section (OR: 1.2; CI: 1.1-1.4) and to a lower probability of having a spontaneous labour (OR: 0.9; CI: 0.7-0.9) and a spontaneous delivery (OR: 0.8; CI: 0.7-0.9). In contrast, a high MSSS score had a lower likelihood of ceasing breastfeeding before 6 months (OR: 0.8; CI: 0.7-0.9) and caesarean section(OR: 0.8; CI: 0.7-0.9) and higher likelihood of spontaneous onset labour (OR: 1.2; CI: 1.1-1.3) and spontaneous delivery (OR: 1.2; CI: 1.1-1.4).
Conclusions. *Pregnancy, childbirth and maternity outcomes are strongly influenced and conditioned by the social context in which they occur and the support the woman may receive. The presence or lack of this support may affect the health of newborns.*

Background

On 23 May 2018 in Geneva, WHO, Unicef, the World Bank and the Maternal and Child Health Partnership wrote the document "nurturing care for early child development: a global framework action" [1]. It represents a milestone in a more than two decades long journey during which a growing body of scientific evidence in different disciplinary fields, from neuroscience to economics, has fundamentally changed the way early child development (ECD) is understood, making us realise the damage caused by the lack of opportunities to develop to their full potential in the early years, the benefits of early intervention, and therefore the need to invest more in health, nutrition, early education, social protection in this crucial period of life [2].

The period from pregnancy to age 3 is when children are most susceptible to environmental influences [3]. That period lays the foundation for health, well-being, learning and productivity throughout a person's whole life, and has an impact on the health and well-being of the next generation [4, 5].

A new-born baby's brain contains almost all the neurons it will ever have. by age 2, massive numbers of neuronal connections have been made in response to interactions with the environment, and especially interactions with caregivers [6]. This is a useful window of opportunity to lay the foundations of health and wellbeing whose effects will last a lifetime and will also be reflected in the next generation [7].

Children who do not have the opportunity to receive appropriate nurturing care during the very early years of life are more likely to have learning difficulties at school and consequently be less productive in the future. This negatively influences the well-being and prosperity of their families and societies [8, 9].

This happens through a process called epigenetics [10, 11]. Epigenetic intervention does not take place through intervention on the DNA, but on its structure. In this way, the DNA can remain quiescent, only to be faithfully transcribed when needed [12]. Unlike mutations, which involve a change in the nucleotide sequence of DNA, the epigenetic phenomenon influences gene expression without altering the sequence [13]. The most frequent epigenetic interventions are carried out by cutting or adding 2 small chemical groups: methyl (present on DNA and histones) or acetyl (present only on histones) [10, 14]. Demethylation and acetylation

result in structural remodelling of the nucleosome and subsequent transcription. These epimutations last throughout the life of the cell and can thus be passed on to subsequent generations through cell divisions [10, 14]. Thus, the environment to which a child is exposed during the first thousand days of life can condition its future growth [11].

Growing up in an optimal environment, from pregnancy to the third year, is particularly important for physical, emotional, social and cognitive development. Conversely, a negative environment impairs development, both in the short term and, more importantly, in the long term. Continuous adversity negatively influences the psychological and neurological development of young children [15, 16]. When pregnancy problems lead to low weight or prematurity, the risk of developmental problems and chronic diseases in adulthood increases [4]. Other factors that threaten early child development include inadequate maternal nutrition, exposure to environmental pollutants and toxic chemicals, mental health problems in caregivers, inadequate breastfeeding, malnutrition, illness, violence experienced, inadequate stimulation, neglect, maltreatment, disabilities, and violence at home and in the community [4]. Discrimination between boys and girls can also have negative effects on children's development in these early years [17]. It is very difficult for families to provide care for their children when they are in extreme poverty or struggling for survival [18]. These adverse situations and lack of support can compromise the ability of families to provide adequate nurturing care for their children [1].

Indeed, women with low social support in pregnancy are more likely to have a worse health status, to seek medical help more often and to experience postpartum depression more frequently [19].

Starting from the assumption that the first 1000 days are crucial for the health of the child and the well-being of the mother-child dyad, the aim of the study is to investigate how social support can influence the course of pregnancy and motherhood.

Materials and methods

The retrospective observational study was conducted on a sample of mothers living in Italy or abroad, enrolled through various groups present on social networks, to which a questionnaire in Italian was administered ad hoc from July to September 2021. The questionnaire consists of 37 questions, 11 of which analyse socio-demographic variables, 20 concerning current and any previous pregnancies and breastfeeding, and 6 that are part of the validated questionnaire used to calculate the Maternity Social Support Scale (MSSS).

The questionnaire used contained the following variables:

- **Socio-demographic characteristics**: Age, nationality, educational qualification, current profession, marital status;
- **Obstetrical data**: Parity, desired/expected motherhood, did she ever suffer from anxiety or depression, mode of delivery, whether planned or urgent caesarean section, onset of labour (spontaneous/induced), breastfeeding and for how many months;
- **Social Support**: Maternity Social Support Scale (MSSS)-Webster et al, 2000 [20].

The MSSS contains six items and includes questions on family support, friendship network, help from spouse, conflict with spouse, feeling controlled by spouse, and feeling unloved by spouse (Tab. I). Each item was measured on a five-point Likert scale and a total score of 30 was possible. We classified social support in to three categories: high social support (for scores 23–30), medium social support (15–22) and low social support (below 14) categories. The internal consistency of the scale was tested using Cronbach's alpha and was found to be 0.74.

Data analysis

Data were analyzed using STATA Version 14. First, frequency distributions of the characteristics of study population were tabulated.

Subsequently, a bivariate analysis was performed to compare MSSS score with the variables concerning childbirth and lactation by means of Chi-square tests. To see how much the score influenced pregnancy and lactation outcomes, the ODDs Ratio was used.

Results

The sample consisted of 3447 women. The demographic and obstetrical data are shown in the Table II.
Concerning the current maternity and pregnancy, 88.02% declare that they desired it and 63.53%
The majority of our sample breastfed. Analysing the data

Tab. I. Maternity Social Support Scale (MSSS).

Statements	Never	Rarely	Some of the time	Most of the time	Always
I have good friends who support me	1	2	3	4	5
My family is always there for me	1	2	3	4	5
My husband/partnet helps me a lot	1	2	3	4	5
There is a conflict with my husband/partner	5	4	3	2	1
I feel controlled by my husband/partner	5	4	3	2	1
I feel loved by my husband/partner	1	2	3	4	5

Tab. II. Demographic and obstetrical data.

Variabile	N	%
Age		
15-20	25	0.7
21-25	247	7.2
26-35	2034	59
36 e 45	1095	31.8
> 45	46	1.3
Residence		
North	1335	38.7
Centre	965	28
South	730	21.2
Islands	357	10.4
Abroad	60	1.7
Education		
Primary school	12	0.3
Lower secondary school	406	11.8
Secondary school	1672	48.5
University degree	954	27.7
Specialisation/master's degree	403	11.7
Job		
Housewife	734	21.3
Unemployed	456	13.2
Self-employed	369	10.7
Employee	1578	45.8
Student	43	1.3
Part time	267	7.8
Civil status		
Single	191	5.5
Married	1937	56.2
Cohabiting	1260	36.5
Separated/divorced	58	1.7
Widowed	1	0
Number of children		
1	877	25.4
2	752	21.8
3	162	4.7
4	37	1.1
5	6	0.2
no answer	1613	46.8
Breastfeeding		
yes	2957	85.8
no	490	14.2
Months breastfeeding		
Still breastfeeding	37	1.1
1-6	613	17.8
7-12	423	12.3
>12	904	26.2
no answer	1470	42.7
Diseases		
Anxiety	630	18.3
Depression	228	6.6
Eating problems	216	6.3
Chronic Diseases	327	9.5
Other	450	13.1
No answer	1596	46.3
Delivery		
Spontaneous	2181	63.3
Caesarean section	1028	29.8
Operative	238	6.9
Labor		
Spontaneous	1844	53.5
Induced	1099	31.9
No answer	504	14.6

of women who did not breastfeed, it appears that: and 10.47% declared that they could not do so due to clinical reasons; 5.11% answered that they did not feel able to do so. 28.89% stopped breastfeeding within 6 months.

Our sample answered the questions concerning the maternity social support scale according to Table III.

For the item "I have good friends who support me", most of our sample answered "some of the time".

For the item "my family is always there for me", most of our sample answered "always".

For the item "my husband/partner help me a lot", most of our sample answered "always".

For the item "There is a conflict with my husband/partner", most of our sample answered "some of the time".

For the item "I feel controlled by my husband/partner", most of our sample answered "never".

Finally, to the item "I feel loved by my husband/partner", most of our sample answered "always".

The mean of the Maternity Social Support Scale (MSSS) was calculated to be 23.91 points (CI 23.80-24-03).

The breastfeeding variable gave a statistically significant difference when compared with:

- the item "My husband/my partner helps me a lot" ($p < 0.01$);
- the item "There is conflict with my husband/partner" ($p < 0.05$).

The variable when she stopped breastfeeding her first child gave a statistically significant difference when compared with:

- the item "I can always count on my family" ($p < 0.05$);
- the item "I feel controlled by my husband/partner" ($p < 0.01$).

To investigate the variability of pregnancy and maternity outcomes in relation to the MSSS score, we divided our sample into 3 score classes:

- 54 women scored < 14;
- 976 women scored between 15 and 22;
- 2417 women scored between 23 and 30.

No statistically significant correlations were found with the score between 7 and 14 due to the low number of our sample with this score.

On the other hand, the relationships in Table IV were found to have a medium and high score.

Those with a medium score are more likely to stop breastfeeding before 6 months, to have no labour and spontaneous delivery and to have no caesarean section.

Those with a high score are more likely to breastfeed more than 6 months, to have labour and spontaneous delivery and to have no caesarean section.

Discussion

The aim of our study was to investigate how social support influenced pregnancy and motherhood.

Almost all of the women in our sample were married or lived with the father of the child, so they almost had family stability and most wanted the current pregnancy. Most of them breastfed, but it is important

Tab. III. MSSS answers.

Statements	Never		Rarely		Some of the time		Most of the time		Always	
	N	%	N	%	N	%	N	%	N	%
I have good friends who support me	171	4.96	455	13.20	1249	36.23	797	23.12	775	22.48
My family is always there for me	59	1.71	163	4.73	521	15.11	834	24.19	1870	54.25
My husband/partner helps me a lot	65	1.89	151	4.38	662	19.21	956	27.73	1613	46.79
There is a conflict with my husband/partner	657	19.06	1138	33.01	1309	37.98	156	4.53	187	5.43
I feel controlled by my husband/partner	1773	51.44	748	21.70	759	22.02	87	2.52	80	2.32
I feel loved by my husband/partner	75	2.18	85	2.47	374	10.85	898	26.05	2015	58.46

Tab. IV. Odds ratio and MSSS

	MSSS scores 15-22		
Variable	OR	C.I.	p
Breastfeeding < 6 months	1.24	1.07 – 1.44	0.01
Spontaneous labor	0.86	0.74-0.98	0.05
Spontaneous delivery	0.83	0.71-0.96	0.05
Cesarean section	1.22	1.04-1.43	0.05
	MSSS scores 23-30		
Variabile	OR	C.I.	p
Breastfeeding < 6 months	0.81	0.70 – 0.94	0.01
Spontaneous labor	1.16	1.01-1.34	0.05
Spontaneous delivery	1.2	1.04-1.40	0.05
Cesarean section	0.82	0.70-0.96	0.05

to underline that a small proportion did not feel able to do so. It is safe to assume that if these women had had adequate support, not only from their family, partner or health personnel, but also from social networks themselves, they would have been able to breastfeed [21-24]. The same applies to the small percentage of women who stopped breastfeeding early (by 6 months) [21, 23].

Concerning the variables of the maternity social support scale, the majority of our sample always has their family or husband/partner to count on, thus an important and always present support. On the other hand, it should be noted that 167 women feel controlled by their husband/partner always or most of the time. This should set an alarm bell for possible violence within the family unit, which will then affect not only the pregnancy but also the puerperium [21].

However, the average score on the maternity social support scale is high, indicating good support. It is important to highlight the statistically significant relationships between breastfeeding with the variables concerning the support received from the family and the relationship with one's husband/partner. This result confirms the data in the literature on the subject of how support from the husband/partner can also influence breastfeeding [22, 24-26]. To emphasise the importance of this support, the odds ratio also shows that a low to medium score correlates with a higher probability of stopping breastfeeding before 6 months, a lower chance of spontaneous labour and delivery and a higher probability of caesarean section.

We know that the social support perceived by mothers during pregnancy plays a significant role as a protective factor against postpartum depression, both directly and indirectly, by reducing the negative clinical aspects of the childbirth experience [27].

Our findings regarding social support and type of childbirth are in line with those found in the literature [28-31].

The limitation of this study is that the women who participated were enrolled online, so women who are young, have an internet connection and know how to use social networks, and are therefore not representative of the general population. These are women who are also able to receive support from other mothers through social networks.

Conclusions

The results showed that most of our sample had good social support. The outcomes of pregnancy, childbirth and motherhood are strongly influenced and conditioned by the social context in which they occur and the support the woman can receive. The presence or lack of this support can affect the health of newborns. The role that all sectors, including the health sector, must play in supporting the optimal development of all children is important. An enabling environment is needed: policies, programmes and services that provide families, parents and caregivers with the knowledge and resources to ensure adequate nurturing care for their children.

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Conflict of interest statement

The authors declare that they have no conflict of interests

Authors' contributions

All Authors made substantial contributions to the concept and design, analysis and interpretation of data, and drafting and revisions.

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Use of medicines to alleviate negative emotional states among adolescents attending Special Education Centres

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Keywords

Medicines for negative emotional states • Prevalence • Risk/protective factors • Youth • Special Educational Centres

Summary

Introduction. *Substantial research evidence indicates that adolescents commonly use a variety of pharmaceuticals. Studies in this area carried out so far in Poland have focused on youth attending mainstream schools. However, there is a lack of research covering adolescents residing in special education centres (SEC). The purpose of the study was to assess the prevalence of medicine use for negative emotional states (nervousness, difficulties in falling asleep, and depressive mood), and to identify factors associated with the use of the aforementioned medications by SEC youth.*
Materials and methods. *The study was conducted in 2018 on a random nationwide sample of SEC adolescents aged 12-19 (N = 1730). The logistic regression analyses included sociodemographic variables, as well as factors related to the participant's individual characteristics and to their social environment.*

Results. *Medicine use for negative emotional states was confirmed by about 24%-30% of respondents. The prevalence of these medicine use among SEC youth was significantly higher than among adolescents from mainstream schools. The individual risk factors associated with medicine use were gender (female), current mental and somatic health problems, past suicide attempts and psychoactive substances use while self-control turned out to be protective factor. Among factors related to the respondents' social environment, positive relationships with peers were significant protective factor.*
Conclusions. *Preventive measures aimed at SEC youth should be focused on improving positive relationships with peers and developing self-control. Educational programs for youth, their parents and SEC staff to develop knowledge and skills regarding safe medicines intake would also be useful.*

Introduction

Research on adolescent medicine use has been undertaken for many years, both as part of international projects [1, 2] and studies conducted in individual countries in Europe, Asia, Africa, America and Australia [3]. Data collected to date indicate that significant percentages of young people take a variety of pharmaceuticals, with the most common being analgesics, cough and cold medicines, antiallergics, dermatological products' as well as vitamins and dietary supplements and antibiotics [3, 4]. Less common is the use of medicines to alleviate negative emotional states, like difficulties in falling asleep, nervousness or depressive/bad mood [1, 2, 5].

It is known from the studies conducted to date that specific factors associated with schoolchildren's medicine use taken to relieve negative emotional states are: sociodemographic status [6,7], self-rated mental health [2, 8, 9, 10], somatic complaints [8, 9], psychoactive substances use like tobacco and alcohol [9, 11], and experience of violence [9, 12]. There are also studies indicating an association between medication for mental health problems use and impulsivity [13]. In addition, some studies confirm that the use of medication to alleviate psychological problems is more common among girls [7]. On the other hand, there are also data indicating that there are no significant differences between boys and girls in the prevalence of medicines taken for difficulties in falling asleep, nervousness, and depressive or bad mood [2, 5]. Young people receive medicines, including those to counteract negative emotional states, primarily from their parents, mainly their mothers [3, 14]. It is also shown that sometimes peers are also the "source" of medicines [15]. It will therefore be interesting to see whether the quality of relationships with parents and friends is related to medicine use among youth.

Studies on medicine use and self-medication have been conducted among adolescents attending mainstream schools and university students [1, 2, 5, 13]. To the best of our knowledge, no research has yet been conducted on this issue among adolescents who, for various reasons, do not attend mainstream educational institutions.

In Poland, young people with elevated level of externalizing problems (*e.g.*, failure to perform school duties, psychoactive substances use, aggression, recurrent conduct problems, antisocial tendencies) and/ or internalizing problems (*e.g.*, depressive disorders, anxiety disorders) cannot continue their education in mainstream schools and are usually referred to Special Educational Centres (SEC), *i.e.* Youth Sociotherapy Centres (YSC) and Youth Correctional Centres (YCC) [16, 17].

YSC are intended for young people who, due to the externalizing and/or internalizing problems mentioned

above, have been deemed at risk of social maladjustment. Young people are placed in YCC at the request of their parents or legal guardians, but a psychological-pedagogical counselling centre's decision on the need for special education is required.

Youth Correctional Centres are designed for socially maladjusted adolescents who require specially arranged learning methods and strategies to re-socialization into society. The basis for placing a teenager in an YCC is a decision issued by the Family and Juvenile Departments of the District Courts [16].

As mentioned above, there is a lack of studies on the prevalence and determinants of medicine use among adolescents in special education facilities, although studies are available on other psychoactive substances like alcohol, tobacco and illicit drugs [18-21]. The purpose of this article is to fill this gap.

The specific objectives of the analyses were:

- to estimate the frequency on medicine use to relieve negative emotional states as difficulties in falling asleep, nervousness, depressive or bad mood among youth attending SEC;
- to analyse the associations between these medicine use and selected socio-demographic variables (gender, family structure, type of educational institution), mental and somatic health variables (current mental and somatic health problems, suicide attempts), psychoactive substance use variables (alcohol, nicotine, novel psychoactive substances, NPS), and other psychosocial variables (self-control, peer relationships, experiencing peer violence, and parental monitoring of adolescent behaviour).

Materials and methods

Sample selection and study implementation

The study involved youth from randomly selected YSC and YCC. Approximately 40% of the centres operating in Poland were drawn (30 YSC and 35 YCC). Due to the lack of consent from some of the centres (9 directors refused, with the reason being the lack of parental consent in two cases), their pool was supplemented by 10 centres outside the originally drawn sample. In the end, the study included students from 25 YSC and 39 YCC. The surveys were conducted by trained interviewers from outside the SEC, with procedures ensuring the anonymity of individual students, classes and centres. The traditional paper-pencil survey was completed by 2,063 students, accounting for 76% of the drawn sample. The data of 333 participants were excluded from analyses due to significant missing data or responses, drawings or vulgar comments indicating that the study was not taken by them seriously.

Measurements

The questionnaire consisted of questions and scales used and psychometrically tested in previous studies conducted among adolescents in Poland [22]. In order to verify the understanding of the design and vocabulary used in the questions, and to possibly adapt the questionnaire to the language and experiences of SEC students, qualitative and quantitative pilot study was conducted prior to the nationwide study. The aim of this pilot study was also to verify if the questions included in the survey did not violate the sense of security of the participants. Detailed information on the method can be found in an earlier publication [23].

Dependent variable

- Frequency of medicine use. Three questions related to the monthly frequency of medicine use due to: 1) difficulties in falling asleep, 2) nervousness (irritability), 3) depressive/bad mood (sadness). Participants were given a choice of 7 responses ranging from "1" = "I did not use" to "7" = "40 times or more" These questions were adapted from the Health Behaviour in School-aged Children (HBSC) study and modified by the research team [5]. An indicator of frequent medication use was the use of the listed pharmaceuticals at least 1-2 times in the last month.

Independent (explanatory) variables

Youth mental health
- Current mental and somatic health problems: two questions developed by the US Centers for Disease Control and Prevention (CDC) related to: 1) feeling depressed, stressed and experiencing emotional problems (deteriorated mental health); 2) physical illness or injury (deteriorated somatic health). Respondents entered the number of days in the last month that they experienced that kind of problems [24].
- Suicide attempts: A single question about ever having attempted suicide in their lives, with responses ranging from "1" = "no" to "4" = "yes, three or more times" [authors' own elaboration].

The frequency of psychoactive substance use
- Cigarette smoking: one question elaborated in the authors' previous studies on the frequency of current (within the last year) smoking of traditional cigarettes, with answers to choose from "1" = "no" to "5" = "yes, daily." [25].
- Alcohol use: a single question adopted from the European School Survey Project on Alcohol and Other Drugs (ESPAD) on the frequency of alcohol use in the last 30 days before the survey, with answers ranging from "1" = "I didn't drink" to "7" = "40 or more times." [26, 27].
- Cannabis use: a single question taken from ESPAD on smoking marijuana/hashish in the last 30 days before the survey, with responses ranging from "1" = "I have not used" to "7" = "40 or more times." [26, 27].
- Novel psychoactive substance (NPS) use: a single question on so-called "legal highs" use in the last 30 days before the survey, with answers ranging from "1" = "I have not used" to "7" = "40 or

more times" [authors' own elaboration on ESPAD questionnaire].

Other psychosocial variables
- Impulsivity *vs* self-control: an abbreviated version of the Barratt Impulsivity Scale (BIS-11), consisting of 7 statements related to diligence in task planning, ability to concentrate and deliberate, inconsiderate behaviour and difficulty in concentrating, with responses ranging from "1" = "never or rarely" to "4" = "almost always or always" [28, 29]. The internal consistency of this scale was acceptable (Cronbach's α = 0.70).
- Experiencing violence: a single question taken from The Ontario Student Drug Use and Health Survey (OSDUHS) about experiencing violence in the past 12 months, with responses ranging from "1" = "never" to "4" = "daily or almost daily" [30, 31].
- Experiencing cyberbullying: a single question developed by Pyżalski on experiencing regular and over an extended period of time harassment from classmates using the Internet or a cell phone, respondents were given a choice of answers ranging from "1" = "never happened" to "4" = "happened 4 or more times." [32].
- Parental monitoring: a scale taken from the Flint Adolescent Study containing 8 statements related to parental monitoring of where the adolescent spends his or her free time, including time spent online and who his (or her) peers are, with responses ranging from "1" = "never" to "5" = "always" [22, 33]. The internal consistency of this scale was high (Cronbach's α = 0.91).
- Positive relationships with peers: a scale developed by the authors in an earlier study consisting of 6 questions related to the relationships with peers and self-efficacy in interactions with classmates, like the ability to persuade or express opinions when others disagree, with responses ranging from "1" = "not at all" to "4" = "definitely yes" [34] (Cronbach's α = 0.94).

STATISTICAL ANALYSES

Differences in the prevalence of medicine use were analysed using the chi-square test, with a commonly accepted significance threshold of $p < 0.05$. The nonparametric Mann-Whitney U test and logistic regression analysis with Wald backward elimination were used to analyse the associations between medicine use and selected variables. For the logistic regression analysis, a dichotomous dependent variable was used, which referred to medicine use for negative emotional states at least 1-2 times in the last month (a combined indicator for medications for falling asleep, nervousness and depressive or bad mood states): 1 = used medicines in the last month, 0 = never happen in the last month. Sociodemographic factors in the regression model were coded as follows:
- gender (1 = girls, 2 = boys);
- type of centre (1 = YSC, 2 = YCC);
- family composition (1 = both parent family, 2 = single parent family).

The psychosocial variables included in the logistic regression model were quantitative. The exception was the variable related to suicide attempts, which took the value 1 = no suicide attempts *vs* 2 = yes, one time or more often.

Multivariate regression analysis required a complete data set – missing data were imputed by the multiple imputation (MI) method recommended in the literature for this purpose [35]. The SPSS 17.0 statistical package was used for all analyses.

As noted in the introduction section, there is a lack of research on medicine use among adolescents attending special education institutions. However, it is known that the prevalence of substances like alcohol, tobacco and illegal drugs is significantly higher among these adolescents than among adolescents from mainstream schools [21]. Therefore, it became interesting to see how the prevalence of medicine use among adolescents in SEC differs from the prevalence among of adolescents from "regular" schools. For comparative purposes, we used data from the 2016 Mokotów study, conducted among 15-year-old students from Warsaw schools [36]. The question on medicine use applied in the Mokotów study is almost identical to the question used in the present study. Due to age differences between the participants of the two surveys, only data from younger participants in the SEC surveys, *i.e.*, adolescents aged 12-15, were used for the comparison.

Results

CHARACTERISTICS OF THE STUDY PARTICIPANTS

The study included 1,730 SEC students, the majority of whom (67.2%) were boys, which reflects the actual gender distribution in this type of institutions (Table I). Respondents from YCCs predominated in the survey sample, which is also in line with the actual state, since at the time the project was implemented, there were about 5,000 students in YCC, while about 4,000 students in YSC facilities. Data on the family composition and the parents' education indicate that the situation of adolescents residing in SEC differs from that of adolescents attending mainstream schools. First of all, the majority of respondents in our study (66.9%) confirmed that they came from single-parent families, with girls giving this answer slightly more often than boys. Data on the families of students from "regular" schools, on the other hand, indicate that the majority of these adolescents (approximately 77%), live with both parents [37].

The data collected in the present study further indicates that the young people in SEC come from families with lower-than-average levels of education. According to our respondents' knowledge, only about 10% of mothers and 7.5% of fathers had a university degree. Nationwide data, on the other hand, indicate that about 23.5% of adult Poles – including approximately 18% of men and 29% of women – graduated from higher education [38]. It should be noted, however, that due to numerous answers

Tab. I. Descriptive information on the study population.

	Girls N = 565 (%)	Boys N = 1159 (%)	Total N = 1730 (%)
Age			
12-15 years	233 (41.3)	447 (38.8)	682 (39.6)
16-19 years	331 (58.7)	704 (61.2)	1039 (60.4)
Type of centre			
Youth Sociotherapy Centre (YSC)	197 (34.9)	459 (39.6)	662 (38.3)
Youth Correctional Centre (YCC)	368 (65.1)	700 (60.4)	1068 (61.7)
Family composition			
both parents family	159 (28.3)	407 (35.5)	567 (33.1)
single parent family or step parent family	402 (71.7)	738 (64.5)	1145 (66.9)
Mother education			
primary or vocational education	218 (39.2)	408 (35.9)	630 (37.1)
secondary education	100 (18.0)	243 (21.4)	345 (20.3)
university degree	70 (12.6)	99 (8.7)	169 (10.0)
I do not know or I have no mother	168 (30.2)	385 (33.9)	553 (32.6)
Father education			
primary or vocational education	176 (32.0)	361 (32.1)	539 (32.1)
secondary education	74 (13.5)	158 (14.1)	233 (13.9)
university degree	47 (8.5)	79 (7.0)	126 (7.5)
I do not know or I have no father	253 (46.0)	526 (46.8)	781 (46.5)

Missings ranged from 0.3% to 3.0%

and responses indicating that the study participants have no parents (or have no contact with them), data on the education of respondents' mothers and fathers is not precise.

MEDICINE USE

Medicine use for negative emotional states was confirmed by approximately 25% of respondents, including 25.8% who used medications for difficulties in falling asleep, 29.8% for nervousness and 23.9% for depressive or bad mood. All of the aforementioned pharmaceuticals were used significantly more often by girls than boys (Tab. II).

A summary of medicine use prevalence among SEC youth and participants of the Mokotów study conducted at mainstream schools indicates that the prevalence of all pharmaceuticals is significantly higher among SEC adolescents, with the greatest differences noted for

tranquilizer use among girls (more than 23 percentage points) (Fig. 1).

MEDICINE USE ACCORDING TO VARIABLES INCLUDED IN THE STUDY

Table III presents the comparisons of medicine use for negative emotional states according to sociodemographic variables and dichotomized values of individual and social factors. Of the sociodemographic variables, medicine use was significantly differentiated only by gender, with girls using these medicines more often than boys. Medicine use was also significantly differentiated by individual and social factors – with the exception of cigarette smoking (p = 0.150) and parental monitoring of the adolescent's behaviour (p = 0.953). Medicines were used more often by SEC students that confirmed medium or high intensity of: current mental and somatic health problems, substance use, experiencing violence

Tab. II. Medicine use for negative emotional states prevalence among SEC youth (use at least 1-2 times in the last 30 days).

		YSC N = 662 (%)	YCC N = 1068 (%)	Total N = 1730 (%)
Difficulties in falling asleep	Girls	65 (33.3)	104 (28.5)	169 (30.2)
	Boys	99 (22.0)	170 (24.7)	269 (23.6)*
	Total	167 (25.6)	274 (26.0)	441 (25.8)
Nervousness	Girls	76 (39.2)	124 (34.7)	200 (36.3)
	Boys	123 (27.6)	176 (25.7)	299 (26.4)**
	Total	203 (31.4)	300 (28.8)	503 (29.8)
Depressive or bad mood	Girls	63 (32.1)	110 (30.3)	173 (30.9)
	Boys	97 (21.7)	136 (19.7)	233 (20.4)**
	Total	162 (24.9)	246 (23.3)	408 (23.9)

* p < 0.05; ** p < 0.01 (comparison between girls and boys).
Missings ranged from 0.9% to 3.0%

Fig. 1. Summary of the medicine use prevalence among SEC students (younger group 12-15-year olds) and among the 2016 Mokotów Study respondents (medicine use at least 1-2 times in the last 30 days, in percents).
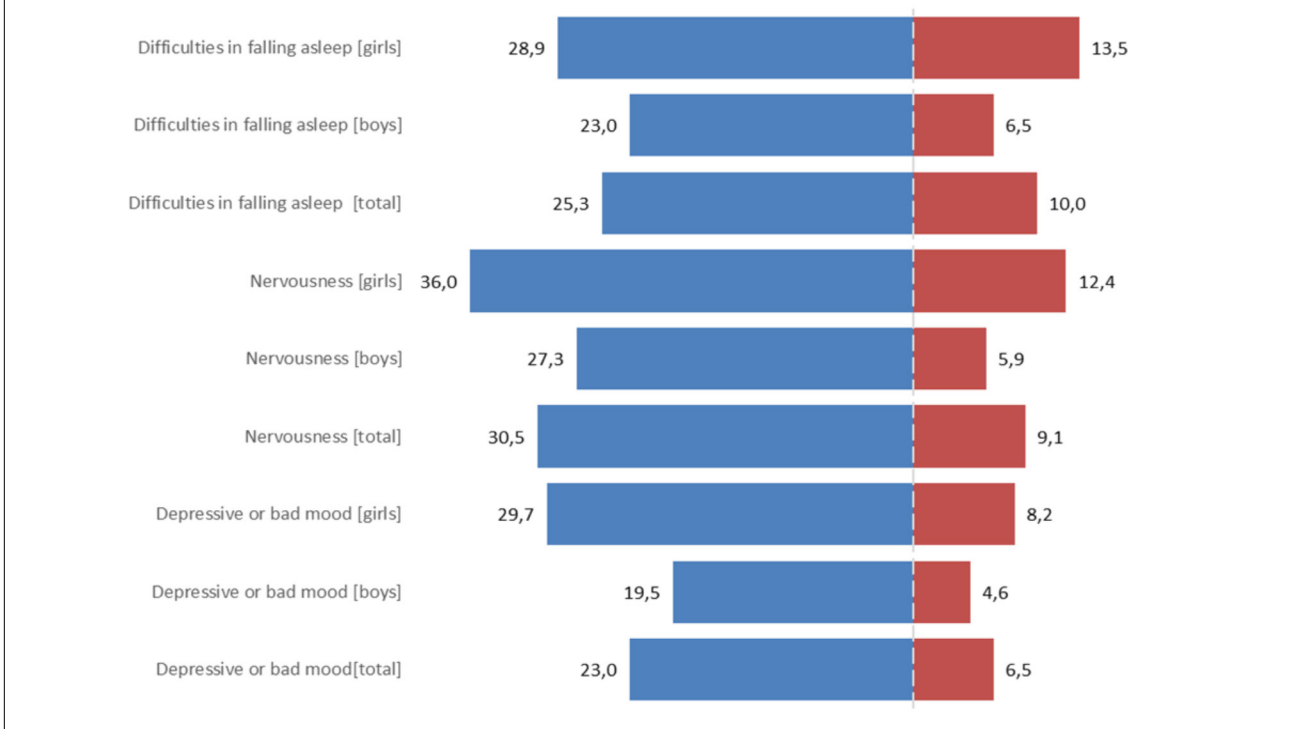
and cyberbullying, and having a history of suicide attempts. Higher (average or above average) intensity of self-control and positive relationships with peers were associated with less frequent medicine use.

ANALYSIS OF THE RELATIONSHIP BETWEEN MEDICINE USE AND SELECTED VARIABLES

Logistic regression analyses identified factors that increase the risk of medicine use after controlling for sociodemographic variables (gender, the type of facility and the family composition) (Table IV).

All analysed variables related to the participants' health turned out to be risk factors for medicine for negative emotional states use, *i.e.*, experiencing current mental health problems (OR 1.02; 95% CI: 1.00-1.03), somatic health problems (OR 1.02; 95% CI 1.01-1.04) and past suicide attempts (OR 1.57; 95% CI: 1.24-2.00). The use of other psychoactive substances, including drinking alcohol (OR 1.11; 95% CI: 1.04-1.18) and NPS use (OR 1.15; 95% CI: 1.03-1.28), were also associated with medicine use. In contrast, the factor that protects against medicine use was self-control (OR 0.75; 95% CI: 0.61-0.93). Of the factors related to the respondents' social environment only positive relationships with peers appeared to be significant and protective (OR 0.71; 95% CI 0.60-0.83).

Discussion

Taking medicines for negative emotional states is much more prevalent among girls and boys residing in SEC facilities than among adolescents attending mainstream schools. This is evidenced by summary the data collected as a part of this project with the results of the Mokotów study conducted in 2016 among Warsaw 15-year-old students [36]. Compared to participants of this study, the percentages of SEC students that confirmed frequent (at least 1-2 times in the last month) medicine user due to difficulties in falling asleep, nervousness, depressive or bad mood were several times higher.

The prevalence of the medicines in question was slightly higher among girls than among boys at SEC facilities. Differences by gender, however, were found to be insignificant in logistic regression analyses. This indicates that, as in the general population of adolescents, gender is not a predictor of taking medication due to negative emotional states [2, 5]. It can be hypothesized that this is related to the mental health problems severity. Studies among adults indicate that although women are more likely than men to use psychotropic drugs, among those diagnosed with severe mental health problems, there are no differences in the percentages of men and women using such medicines [39]. One of the reasons why young people are referred to SEC facilities are mental health problems, hence the lack of significant differences between girls and boys in the prevalence of medications taken due to negative emotional states.

Regression analyses showed that factors favouring the medicine use to alleviate negative emotional states was the experience of currents somatic health problems. Associations between medicine use in question and

Tab. III. Medicine use for negative emotional states among SEC youth according to the dichotomous values of the study variables.

Study variables		N Mean (SD)	Mean range	Medicine use in the past 30 days	
				U Mann-Whitney significance	
Gender	Boys	1159	1.67 (1.22)	829.96	0.000
	Girls	565	2.05 (1.64)	929.24	
Centre type	MOS	662	1.88 (1.45)	884.19	0.167
	MOW	1068	1.74 (1.33)	853.92	
Family composition	Both parent family	567	1.72 (1.25)	856.30	0.989
	Single parent family	1145	1.83 (1.44)	856.60	
Self-control	Low intensity	930	1.92 (1.49)	908.63	0.000
	Medium or high intensity	800	1.65 (1.23)	815.36	
Current mental health problems	No or low intensity	1250	1.65 (1.20)	827.48	0.000
	Medium or high intensity	480	2.18 (1.71)	964.52	
Suicide attempts	No	1046	1.53 (1.04)	794.90	0.000
	At least one attempt	684	2.20 (1.70)	973.46	
Current somatic health problems	No or low intensity	1539	1.72 (1.30)	845.88	0.000
	Medium or high intensity	191	2.38 (1.81)	1023.60	
Cigarette smoking	No or low intensity	563	1.76 (1.34)	843.44	0.150
	Medium or high intensity	1167	1.81 (1.40)	876.14	
Alcohol use in the last 30 days	No or low intensity	1076	1.68 (1.26)	831.98	0.000
	Medium or high intensity	654	2.00 (1.53)	920.65	
Marihuana use in the last 30 days	No or low intensity	1221	1.72 (1.30)	842.95	0.001
	Medium or high intensity	509	1.98 (1.53)	919.59	
NPS use in the last 30 days	No or low intensity	1504	1.73 (1.32)	841.49	0.000
	Medium or high intensity	226	2.27 (1.64)	1025.27	
Experiencing violence	No or low intensity	1202	1.69 (1.24)	841.28	0.001
	Medium or high intensity	528	2.04 (1.62)	920.65	
Experiencing cyberviolence	No or low intensity	1204	1.68 (1.28)	833.56	0.000
	Medium or high intensity	526	2.05 (1.56)	938.61	
Parental monitoring	No or low intensity	869	1.81 (1.41)	864.88	0.953
	Medium or high intensity	861	1.78 (1.35)	866.13	
Positive relationships with peers	No or low intensity	642	1.98 (1.50)	932.11	0.000
	Medium or high intensity	1088	1.69 (1.29)	826.19	

somatic health have also been documented in other studies among adolescents [8, 9]. Also consistent with expectations is the result indicating that experiencing current mental health problems is a risk factor for medicine use for negative emotional states. This association is also confirmed in other studies among adolescents [2, 5, 8].

However, the strongest association appeared to be between the medicine use and the past suicide attempts. Authors of the studies on hospitalizations of young people in Poland due to poisoning indicate that medicines (next to alcohol) are the most common substances used in intentional poisoning of adolescents [40-42]. Among the pharmaceuticals used for that purpose the following are listed: antidepressants, anticonvulsants, antianxiety, antipsychotics, sleeping pills and tranquilizers, but also anti-inflammatory, analgesic and cough medicines – including medications containing dextromethorphan [40-42].

Hospitalizations of adolescents for multi-medicine poisoning or combining pharmaceuticals with alcohol or illegal drugs are also reported [42]. It is also known that adolescents use medications to take their own lives-psychological and/or psychiatric consultations conducted as part of hospitalizations at one children's hospital found that almost half of intentional poisonings (most of which were poisonings caused by medicines) were suicide attempts [40]. In this context, our results indicating an association between medicine use and suicide attempts by the study participants are particularly of sever concern. It is also worth noting that approximately 60% of girls attending SEC facilities confirmed suicide attempts [43], and it is known from other studies that girls are more likely than boys to use medicines for suicidal purposes [44].

Our study does not provide an answer to the question of what specific medications are taken by SEC youth. The Mokotów study cited earlier indicates that among the pharmaceuticals mentioned as medicines used for negative emotional states, respondents most often indicate herbal sedatives and sleeping pills available without a doctor's recommendation – medicines available only by prescription are mentioned sporadically [36]. Unfortunately, we do not have data

Tab. IV. The last step in logistic regression analysis with backward elimination of variables irrelevant to the model (Wald), an explained variable: medicine use for negative emotional states among SEC youth, N = 1706

Variables/category	Wald coefficient	Odds ratio	95.0% Confidence interval		Significance
			Lower	Upper	
Sociodemographic factors (reference group)					
Gender (boys)	0.078	1.035	0.812	1.320	0.780
Centre type (YSC)	0.380	0.933	0.750	1.162	0.538
Family composition (both parent family)	0.087	0.966	0.769	1.213	0.768
Individual factors					
Self-control	7.168	0.753	0.612	0.927	0.007
Current mental health problems	6.315	1.015	1.003	1.028	0.012
Suicide attempts	14.220	1.571	1.242	1.987	0.000
Current somatic health problems	8.647	1.022	1.007	1.037	0.003
Alcohol use in the last 30 days	9.517	1.107	1.038	1.181	0.002
NPS use in the last 30 days	6.181	1.147	1.030	1.279	0.013
Social factors					
Experiencing cyberviolence	3.042	1.120	0.986	1.273	0.081
Positive relationships with peers	18.073	0.706	0.601	0.829	0.000
Constant	0.868	0.668			0.352

on the type of tranquilizers, sleeping pills or anti-depression medications taken by youth attending SEC facilities. However, it can be assumed that the much higher prevalence of mental health problems is reflected by more frequent medicine use available on a doctor's recommendation among SEC youth than among the adolescents in general population.

The questions about medicine use applied in the Mokotów study and the SEC survey are phrased in such a way as to evoke coping with mental health problems. Medicines, however, are also used sometimes for intoxication, but the previous analysis indicate that the percentages of SEC students using various pharmaceuticals for this reason are lower than the percentages of those that use medicines for self-medication. The questionnaire completed by study participants included a question on the narcotics use, among which "psychotropic, sedative, tranquilizers and sleep-inducing medicines" were listed in addition to substances like cannabis, NPS and amphetamines. Taking that kind of medicines (presumably to intoxicate) in the last year before the study was confirmed by 18.5% of younger (12-15 years old) respondents and approximately 24% of older ones (16–19-year-olds) [21].

The question on narcotic substances refers to the last year, while the questions on medicine use refers to the last month. Thus, the result showing that approximately 26% of SEC students used medicines in the last month due to difficulties in falling asleep, while approximately 30% used medicines due to nervousness may indicate that the leading motive to reach for sleeping and sedative medications is the need to cope with negative emotional states.

The association between impulsivity/self-control and medicines for negative emotional states use – namely, the higher the score on the self-control scale, the lower the tendency to use such medications – is confirmed in the

other studies. Indeed, in Canadian study carried out among university students, an association was found between impulsivity and the sedative/tranquilizer, painkillers (opioids), and medications with stimulant effects misuse, while the cited study included only medications available on a doctor's recommendation [13]. According to the authors of that study, the tendency of impulsive people to turn to medications with a variety of effects is a result of the difficulties of controlling behaviours that can bring immediate reward – in this case, relief from psychological ailments [13].

A risk factor for medications use for negative emotional states was also alcohol Thus, it is possible, as some authors have suggested, to consider medicine use as a symptom of unhealthy lifestyle habits [45]. An element of that kind of style may be use a variety of substances, including combining different drugs and – which is particularly risky – mixing pharmaceuticals with alcohol, which, as mentioned above, can become a cause of serious intoxication [40].

The results concerning NPS are in particular interesting as it turned out that these substance use is associated with medicine to alleviate negative emotional states use. As can be surmised, this is related to the properties of sedatives and sleeping pills, which, due to their psychoactive effects – like NPS – are sometimes used for intoxication.

Positive relationships with peers was the only one of the analysed factors related to the participants' social environment that was associated with medicine use – the higher the respondents rated the quality of their relationships with peers, the less likely they were to confirm those pharmaceuticals use. This is an interesting result given previous analyses of SEC data indicating the positive association between good peer relationships and alcohol use and abuse [46]. It is important, however, to remember that adolescent alcohol use is a social

behaviour and is linked to having more friends and higher position among peers [47]. Taking medicines to cope with various psychological problems is an individual experience, although it is known from the previous studies that adolescents share medicines with their peers and colleagues are sometimes perceived as an authority on that matter [15].

The prevalence of medicine use among SEC youth is significantly higher than among adolescents studying in mainstream schools. This can be explained to some extend by the socioeconomic status of SEC youth. Data on the education of the parents of those students indicate that they are less than averagely educated. It is known from the Mokotów study that parental education is a factor associated with adolescent medicine use. Namely, participants in these studies who responded in a questionnaire that their parents had university degree were less likely to endorse medicine for negative emotional states use [5].

Similarly, a Danish study conducted as part of the HBSC project (it is worth remind that the questions about medicine use in the present study were developed based on questions from that project) found that adolescents from families with lower socioeconomic status, which was assessed based on information about their parents' occupation, were more likely to use medicines than their peers from higher-status families [6].

Previous studies do not provide a clear answer to the question of the relationship between families' socioeconomic status and adolescents' medicine use, due to differences in methodology, including different measures of socioeconomic status and medication use. Research evidence suggests, however, that social inequalities in health may not become apparent until adulthood or develop throughout life, hence the inconclusive results of studies conducted among adolescents [6].

Limitations Of The Study

The data presented in this article come from the first nationwide project on the prevalence and determinants of risky behaviour among students from randomly selected SEC institutions which congregate youth that has difficulties in getting education in regular schools. However, the limitations of this project should also be mentioned. The data obtained in the cross-sectional study do not provide a basis for concluding that the relationships found are of a cause-and-effect nature. The use of a questionnaire in which the respondent describes his/her own behaviour and his/her perception of himself/herself and their social environment is, in turn, prone to measurement error due to the imperfections of that research method. Some of the survey questions were related to "sensitive" issues, like substance abuse or mental health problems. Thus, it was to be expected that some students were concerned about the possibility of revealing their answers to SEC staff. To limit this risk, students were assured

that their participation was voluntary, and the survey was conducted with procedures in place to guarantee respondents' anonymity and the confidentiality of the obtained information.

Finally, the summary of data on medicine use among SEC youth with data from the Mokotów study should also be treated with some caution due to differences in sample selection (nationwide *vs* local), the different age of respondents (12-15 *vs* 15) and the two-year difference between the measurements (2018 *vs* 2016).

Conclusions

The study presented here allowed us to conclude that factors associated with medicine by SEC youth are mental health problems, suicide attempts, deteriorated somatic health, as well as the psychoactive substance use, including NPS. Self-control turned out to be protective factor. This indicates that improving knowledge on safe medication use and personal skills of SEC youth, which allow for proper care of somatic and mental health, should be the part of activities in the field of health promotion and prevention. Given that positive relationships with peers were protective factor against medicine use preventive measures at SEC should also be focused on strengthening social relationships.

Very disturbing is the result indicating an association between medicine use and suicide attempts. This proves the need for therapeutic measures aimed at addressing suicide behaviours and other mental health problems among adolescents attending SEC facilities.

Medicine use may also be fostered by adult behaviour – parents and caregivers are the most frequently mentioned in the previous studies as persons who provide medicines to children and adolescents. Therefore, it would be useful to educate parents and SEC staff regarding the administration of various pharmaceuticals and the risks associated with medicine use by children and adolescents without medical supervision.

As already mentioned, the study presented here is part of a project focused on the risk behaviour among SEC youth, the medicine use was measured using single questions about the frequency of taking medications for negative emotional states. Thus, we do not have information on what specific pharmaceuticals our respondents take, whether these are medications they reach for on their own, whether they receive them from adult caregivers or on a doctor's recommendation. The issue of medication use by adolescents residing in SEC facilities therefore requires further research.

Acknowledgments

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Bioethics Committee of the Institute of Psychiatry and Neurology in Warsaw (Poland), Resolution No. 34/2017 of 26 October 2017.

Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Agnieszka Pisarska and Krzysztof Ostaszewski. The first draft of the manuscript was written by Agnieszka Pisarska, all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

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HEALTH PROMOTION

Status of the utilization of preventive care services and its associated socio-demographic factors among Iranian elderly

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Summary

Introduction. *The growing population of the elderly, the rising costs of medical care and the low use of preventive services are three factors that highlight the importance of using preventive health care services in the Iranian population. This study aimed to determine the status of the use of preventive care services and its associated socio-demographic factors in the elderly referred to health centers.*

Methods. *In this analytical cross-sectional study, a number of 160 elderly people referred to health centers in East Guilan, Iran was selected by multi-stage cluster sampling. Data were obtained from May to September, 2021 using a questionnaire containing utilization of preventive care services (9 items) and socio-demographic characteristics.*

Results. *The highest and the lowest utilization rates of preventive care services among study participants were related to the blood pressure test (96.9%) and colonoscopy (17.5%), respec-*

tively. Multivariate analysis showed that only income had a significant association with performing fasting blood sugar test (p = 0.004), blood lipid test (p = 0.004), and blood pressure test (p = 0.013). Also, the associations between having an underlying disease and performing fasting blood sugar test (p = 0.032) and blood pressure test (p = 0.002), the association between gender and performing the bone mineral density test (p < 0.001), and the association between occupation and performing Pap-smear test (p = 0.011), were statistically significant.

Conclusions. *The utilization rates of screening tests for most cancers, including gastrointestinal cancers, were low. Since, there were a significant association between income, disease, gender and occupation with the utilization of some preventive care services, considering them in health centers' preventive care program design might be useful.*

Introduction

Population aging is a global challenge to the world's socio-economic development [1]. Over the last fifty years, socio-economic development, declining fertility followed by diminishing population growth and increasing life expectancy have led to significant changes for the structure of the world's population, so that the number of older people has increased significantly [2]. In 2016, the world's elderly population was about 639 million. Meanwhile, it has been predicted that the number of elderly people will reach about one billion and one hundred million in 2025 [3]. According to the reports provided by the statistics center of Iran in 2016, there are 4,871,518 elderly people in Iran, accounting for 6.1% of the total population [4]. It has been predicted that 20-25% of the Iranian population will be over 60 years of age in 2031 [5].

Although aging is not a disease and achieving old age should be considered as one of the major human advances, nevertheless, the elderly is at increased risk of many chronic diseases (Heart disease, Blood pressure, Diabetes, Arthritis, and Cancer) due to being in a certain area of life [6]. Chronic diseases can lead to hospitalization, long-term disability poor quality of life and death, and they can be a major factor in healthcare expenses [7]. The role of preventive care services has been emphasized in improving the health status of individuals and reducing the financial burden of treatment costs for chronic diseases in the elderly community [8]. Prevention can be considered as one of the most important strategies to achieve healthy and active aging [9, 10].

Use of preventive care has several benefits including, promoting healthy lifestyles, decreasing the chance of becoming disease, treating diseases in early stages, and preventing medical complications [10, 11].

Several studies have attempted to address the issue of low use of preventive care. However, little is known about the factors such as socio-economic inequalities including income, education, gender inequality, and their effect on the utilization of preventive care services [9, 12, 13].

According to the studies conducted in European countries, there is evidence of inequality in the use of preventive care services in favor of groups with a higher socio-economic status [14, 15]. Another study found that women had a higher utilization rate of preventive care services than men [13].

Despite the importance of utilization of preventive care services for the elderly, there are currently few studies in Iran that have examined disease - specific preventive care services [16]. They have also paid little attention to socio-demographic inequalities in the use of preventive care services. Since, any planning for health requires the access of accurate and up-to-date information, it is essential to do studies to assess the utilization of preventive care services and its affecting factors on the Iranian elderly. Therefore, this study investigated the status of utilization of preventive care services and its associated socio-demographic factors on the elderly referred to comprehensive urban health centers in East Guilan.

Materials and methods

STUDY DESIGN AND SAMPLING

The present study was part of a larger analytical cross-sectional research conducted on people 60 years and older referred to the comprehensive health centers in East Guilan (in Northern Iran) between May and September 2021.

Inclusion criteria included age 60 years or older, having a health record in urban comprehensive health service centers, willingness and informed consent to participate in the study and the ability to answer the questionnaire through interviews, and exclusion criteria included obtaining less than 7 points in the short cognitive test

(AMT) [17] and incomplete questionnaire.

The sample size was estimated based on this formula $[z^2_{1-\alpha/2} * p (1-p)]/d2$. Confidence interval was 95%, expected prevalence based on previous study was inserted as 0.28 [16]. The required precision of the estimate (d) was assumed to be 0.08. Then, the design effect of 1.2 and non-response error of 10% was inserted. Finally, 160 people were included in the study.

Participants were included in the study using multistage cluster sampling. First, each city of East Guilan (Astaneh, Lahijan, Rudsar, Siahkal, Langrud) was considered as a cluster. In the next stage, seven out of sixteen comprehensive urban health centers throughout the cities of East Guilan were selected randomly. Then, based on the available population information of each selected centers, the appropriate number of samples were randomly selected proportional to the population of each center according to the total size of the main sample (160 people) (Fig. 1).

MEASUREMENTS

The data collection instrument in this study included a questionnaire consisting of three parts. The first part included the participants' cognitive status test. In this instrument (Abbreviated Mental Test), each correct answer was given a score of 1 while an incorrect answer scored as 0, and the total score was calculated at the end (ranging between 0 and 10). The lower total score indicated a more severe cognitive impairment. In Iran, the validity and reliability of this test were confirmed by Foroughan et al. [18].

The second part included the socio-demographic characteristics of the participants, which included age, gender, marital status, education level, occupation, income, and history of underlying disease.

Fig. 1. Flow-chart of the sampling process and study subject selection.
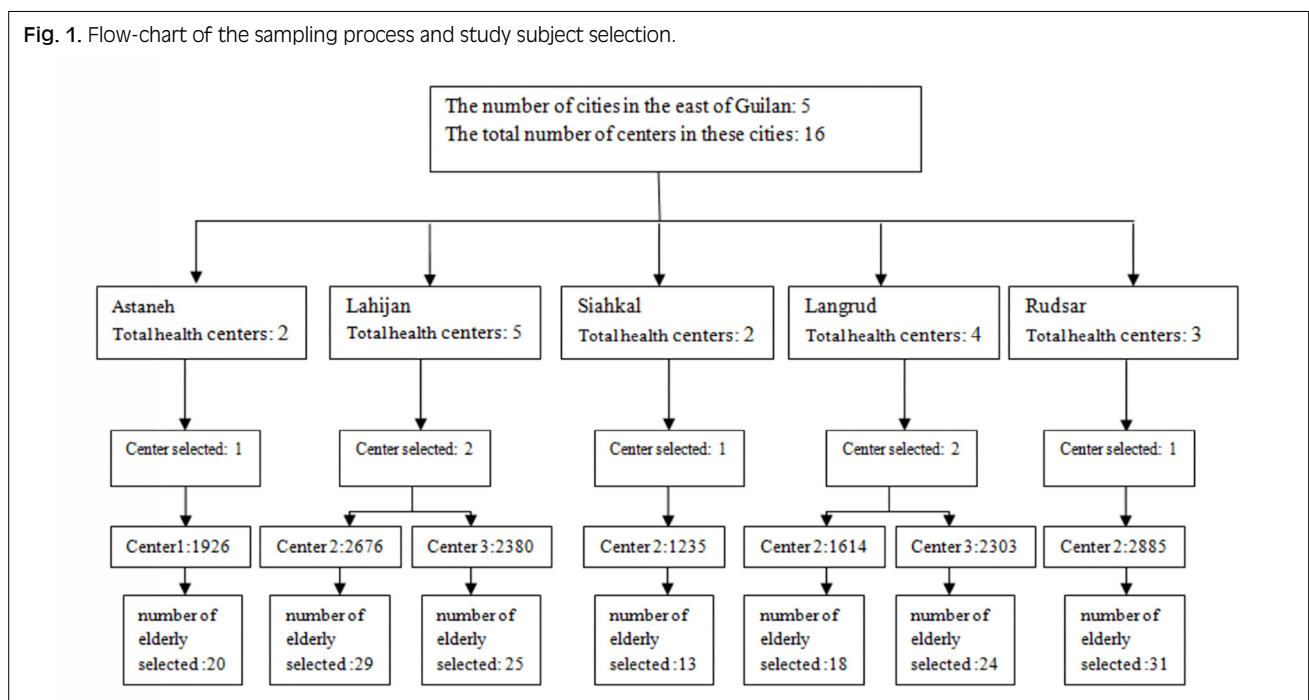
The third part contained nine questions about the utilization of preventive care services, which included fasting blood sugar test, blood pressure test, blood lipid test, fecal occult blood test (over the last 1 year), bone mineral density test (over the last 1 year), prostate-specific antigen (PSA test) in men and mammography and pap-smear tests in women (over the past 5 years) and colonoscopy (over the past 10 years). If the elderly had done any of these tests, they were given a score of 1 otherwise they received a 0 score. They were also asked an open-ended question about the reason for not performing these tests. Content validity (CVI and CVR) of the questionnaire was assessed and approved by 10 members of the nursing and health education faculty members. Then the reliability of the instrument was assessed using the internal consistency method using 30 elderly people. An acceptable value of Cronbach's alpha coefficients was obtained ($\alpha > 0.7$). Due to the pandemic COVID-19, the data were gathered by telephone interview.

DATA ANALYSIS

Descriptive statistics (mean, standard deviation, frequency, and percentage) were used to describe the study population. For the initial review of the association between demographic variables (independent variables) and utilization of preventive care services, the Mann–Whitney, Chi-square, or Fisher's exact tests were used depending on the type of variables (bivariate analysis). Eventually, the significant variables in the bivariate analysis (associated with the utilization of preventive care services) were included in a multiple logistic regression model ($p < 0.05$). The data were analyzed using SPSS version 16.

Results

The information of 160 elderly people (98 females and 62 males) was collected. Mean age and standard deviation of participants was 68.80 ± 6.69. The education level of half of the participants was less than a high school diploma. 124 participants (77.5%) were married and 95% (152) had insurance. Also, less than half of them were unemployed and had a middle income. 81.1% (131) of them had an underlying disease. In addition, the results showed that of the preventive care services, the utilization rate of blood pressure test (96.9%), blood lipid test (88.8%), and fasting blood sugar test (87.5%) were the highest, and the utilization rate of colonoscopy (17.5%), and fecal occult blood test (29.4%) were the lowest among the elderly in this research (Tab. I).

The results of Table II and Table III showed that there were statistically significant associations between the age of the elderly with the utilization of fasting blood sugar test (p = 0.028) and blood lipid test (p = 0.025). The mean age of people who performed blood sugar and blood lipid tests was higher than those who did not. Gender was significantly associated with performing the bone mineral density test (p < 0.001). That is, women were

Tab. I. Demographics characteristics and status of the utilization of preventive care services of research participants (N = 160).

Variable		N	(%)
Gender	Male	62	61.3
	Female	98	38.8
Education	Illiterate	45	28.1
	Lower High school	39	24.4
	High school	45	28.1
	University	31	19.4
Occupation	Unemployed	76	47.5
	Employed	21	13.1
	Retired	63	39.4
Marital	Single	2	1.3
	Married	124	77.5
	Deceased wife	2	1.3
	Divorced	32	20
Insurance	Yes	152	95
	No	7	4.4
	Non-response	1	0.6
Income	Low	42	26.3
	Middle	67	41.9
	High	51	31.9
Disease	Yes	130	81.1
	No	30	18.9
Fasting blood sugar	Yes	140	87.5
	No	19	11.9
	Non-response	1	0.6
Blood lipid test	Yes	142	88.8
	No	18	11.3
Fecal occult blood test	Yes	47	29.4
	No	113	70.6
Blood pressure test	Yes	155	96.9
	No	5	3.1
Bone density test	Yes	67	41.9
	No	93	58.1
Pap-smear test	Yes	37	37.8
	No	61	62.2
Mammography	Yes	46	46.9
	No	51	52
	Non-response	1	1.1
Prostate-specific antigen	Yes	40	64.5
	No	22	35.5
Colonoscopy	Yes	28	17.5
	No	132	82.5
Age	Mean	SD	Min	Max
	68.80	6.69	60	86

more likely to utilize a bone mineral density test than men. Education level, also, had a significant association with the mammography test (p = 0.003). People with a higher education level had a greater rate of mammography use than people with a lower education level. Also, there was a significant association between occupation status and utilizing the Pap-smear test (p = 0.019) and mammography (p < 0.001). People who were employed and retired had a higher utilization rate of Pap-smear test and mammography than unemployed people.

Tab. II. Utilization of preventive services (fasting blood sugar test, blood pressure control, fecal occult blood test, blood lipid test and, bone mineral density test) according to socio-demographic variables of research participants.

Preventive care Variable		Fasting blood sugar			Blood lipid test			Fecal occult blood test			Blood pressure			Bone density test		
		Yes N (%)	No N (%)	P-value	Yes N (%)	No N (%)	P-value	Yes N (%)	No N (%)	P-value	Yes N (%)	No N (%)	P-value	Yes N (%)	No N (%)	P-value
Gender	Female	87 (62.1)	10 (52.6)	0.425*	88 (62)	10 (55.6)	0.599*	33 (70.2)	65 (57.5)	0.133*	96 (61.9)	2 (40)	0.376**	56 (83.6)	42 (45.2)	< 0.001*
	Male	53 (37.9)	9 (47.4)		54 (38)	8 (44.4)		14 (29.8)	48 (42.5)		59 (38.1)	3 (60)		11 (16.4)	51 (54.8)	
Education	Illiterate	39 (27.8)	5 (26.3)	0.709**	40 (28.2)	5 (27.8)	0.725**	13 (27.7)	32 (28.3)	0.961*	44 (28.4)	1 (20)	0.603**	23 (34.3)	22 (23.7)	0.411*
	Lower High school	33 (23.6)	6 (31.6)		33 (23.2)	6 (33.6)		12 (25.5)	27 (23.9)		38 (24.5)	1 (20)		13 (19.4)	26 (28)	
	High school	39 (27.9)	6 (31.6)		40 (28.2)	5 (27.8)		14 (29.8)	31 (27.4)		42 (27.1)	3 (60)		19 (28.4)	26 (28)	
	University	29 (20.7)	2 (10.5)		29 (20.4)	2 (11.1)		8 (17)	23 (20.4)		31 (20)	0 (0)		12 (17.9)	19 (20.4)	
Marital	Single	1 (0.7)	1 (5.3)	0.477*	1 (0.7)	1 (5.6)	0.419*	0 (0)	2 (1.8)	0.323*	1 (0.6)	1 (20)	0.126*	0 (0)	2 (2.2)	0.072*
	Married	108 (77.1)	15 (78.9)		110 (77.5)	14 (77.8)		40 (85.1)	84 (74.3)		121 (78.1)	3 (60)		48 (71.6)	76 (81.7)	
	Deceased wife	29 (20.7)	3 (15.8)		29 (20.4)	3 (16.7)		6 (12.8)	26 (23)		31 (20)	1 (20)		17 (25.4)	15 (16.1)	
	Divorced	2 (1.4)	0 (0)		2 (1.4)	0 (0)		1 (2.1)	1 (0.9)		2 (1.3)	0 (0)		2 (3)	0 (0)	
Occupation	Unemployed	66 (47.1)	9 (47.4)	0.927*	67 (47.2)	9 (50)	0.815*	23 (48.9)	53 (46.9)	0.835*	74 (47.7)	2 (40)	0.208**	34 (50.7)	42 (42.2)	0.198*
	Employed	18 (12.9)	3 (15.8)		18 (12.7)	3 (16.7)		7 (14.9)	14 (12.4)		19 (12.3)	2 (40)		5 (7.5)	16 (17.2)	
	Retired	56 (40)	7 (36.8)		57 (40.1)	6 (33.3)		17 (36.2)	46 (40.7)		62 (40)	1 (20)		28 (41.8)	35 (37.6)	
Insurance	Yes	133 (95.7)	18 (94.7)	1**	135 (95.7)	17 (94.4)	0.576**	46 (97.9)	106 (94.6)	0.675**	125 (96.2)	27 (93.1)	1**	61 (92.4)	91 (97.8)	0.128**
	No	6 (4.3)	1 (5.3)		6 (4.3)	1 (5.6)		1 (2.1)	6 (5.4)		5 (3.8)	2 (6.9)		5 (7.6)	2 (2.2)	
Income	Low	33 (23.6)	9 (47.4)	0.028*	33 (23.2)	9 (50)	0.024*	13 (27.7)	29 (25.7)	0.761*	38 (25.5)	40 (80)	0.011**	12 (17.9)	30 (32.3)	0.101*
	Middle	63 (45)	3 (15.8)		64 (45.1)	3 (16.7)		21 (44.7)	46 (40.7)		67 (43.2)	0 (0)		33 (49.3)	34 (36.6)	
	High	44 (31.4)	7 (36.8)		45 (31.7)	6 (33.3)		13 (27.7)	38 (33.6)		50 (32.3)	1 (20)		22 (32.8)	29 (31.2)	
Disease	Yes	118 (84.3)	11 (57.9)	0.011**	119 (83.8)	11 (61.1)	0.047**	39 (83)	91 (80.5)	0.718*	129 (83.2)	1 (20)	0.005**	58 (86.6)	72 (77.4)	0.144*
	No	22 (15.7)	8 (42.1)		23 (16.2)	7 (38.9)		8 (17)	22 (19.5)		26 (16.8)	40 (80)		9 (13.4)	21 (22.6)	
Age	60-86	Mean (SD) 68.98 (6.52)	Mean (SD) 66.26 (6.90)	P-value 0.028 b	Mean (SD) 68.94 (6.48)	Mean (SD) 66.22 (7.10)	P-value 0.025 b	Mean (SD) 68.23 (6.80)	Mean (SD) 68.81 (6.52)	P-value 0.50 b	Mean (SD) 68.84 (6.58)	Mean (SD) 62.40 (2.88)	P-value a	Mean (SD) 68.88 (6.70)	Mean (SD) 68.46 (6.54)	P-value 0.693 b

* P-value based on Chi-squared test; ** P-value based on Fisher's Exact test; a No statistics are computed because variable is a constant; b P-value based on Mann-Whitney U (age); Significant at 0.05 level.

Tab. III. Utilization of preventive services (PSA test, mammography, Pap-smear and colonoscopy) according to socio-demographic variables of research participants.

Preventive care Variable		Pap-smear test			Mammography			PSA			Colonoscopy		
		Yes N (%)	No N (%)	P-value	Yes N (%)	No N (%)	P-value	Yes N (%)	No N (%)	P-value	Yes N (%)	No N (%)	P-value
Gender	Female	37 (100)	61 (100)	a	46 (100)	51 (100)	a	-	-	a	16 (57.1)	82 (62.1)	0.623**
	Male	-	-		-	-		40 (100)	22 (100)		12 (42.9)	50 (37.9)	
Education	Illiterate	8 (21.6)	23 (37.7)	0.239*	7 (15.2)	24 (47.1)	0.003*	6 (15)	8 (36.4)	0.173**	3 (10.7)	42 (31.8)	0.07*
	Lower High school	10 (27)	14 (23)		11 (23.9)	12 (23.5)		12 (30)	3 (13.6)		9 (32.1)	30 (22.7)	
	High school	12 (32.4)	19 (31.1)		19 (41.3)	12 (23.5)		8 (20)	6 (27.3)		7 (25)	38 (28.8)	
	University	7 (18.9)	5 (8.2)		9 (19.6)	3 (5.9)		14 (35)	5 (22.7)		9 (32.1)	22 (16.7)	
Occupation	Unemployed	17 (45.9)	45 (73.8)	0.019**	20 (43.5)	41 (80.4)	< 0.001**	8 (20)	6 (27.3)	0.737*	9 (32.1)	67 (50.8)	0.198*
	Employed	3 (8.1)	2 (3.3)		4 (8.7)	1 (2)		10 (25)	6 (27.3)		5 (17.9)	16 (12.1)	
	Retired	17 (45.9)	14 (23)		22 (47.8)	9 (17.6)		22 (55)	10 (45.5)		14 (50)	49 (37.1)	
Marital	Single	1 (2.7)	0 (0)	0.208*	0 (0)	1 (2)	0.048*	0 (0)	1 (4.5)	0.194*	1 (3.6)	1 (0.8)	0.436*
	Married	28 (75.7)	38 (62.3)		35 (76.1)	31 (60.8)		39 (97.5)	19 (86.4)		23 (82.1)	101 (76.5)	
	Deceased wife	8 (21.6)	21 (34.4)		9 (19.6)	19 (37.3)		1 (2.5)	2 (9.1)		4 (14.3)	28 (21.2)	
	Divorced	0 (0)	2 (3.3)		2 (4.3)	0 (0)		-	-		0 (0)	2 (1.5)	
Insurance	Yes	33 (89.2)	57 (95)	0.422**	42 (91.3)	47 (94)	0.707**	40 (100)	22 (100)	-	25 (89.3)	127 (96.9)	0.105**
	No	4 (10.8)	5 (3)		4 (8.7)	3 (6)		-	-		3 (10.7)	4 (3.1)	
Income	Low	8 (21.6)	17 (27.9)	0.789*	8 (17.4)	16 (31.4)	0.095*	9 (22.5)	8 (36.4)	0.244*	7 (25)	35 (26.5)	0.355*
	Middle	19 (51.4)	29 (47.5)		22 (47.8)	26 (51)		15 (37.5)	4 (18.2)		9 (32.1)	58 (43.9)	
	High	10 (27)	15 (24.6)		16 (34.8)	9 (17.6)		16 (40)	10 (45.5)		12 (42.9)	39 (29.5)	
Disease	Yes	29 (78.4)	55 (90.2)	0.106*	37 (80.4)	46 (90.2)	0.172*	31 (77.5)	15 (68.2)	0.422*	24 (85.7)	106 (80.3)	0.505*
	No	8 (21.6)	6 (9.8)		9 (19.6)	5 (9.8)		9 (22.5)	7 (31.8)		4 (14.3)	26 (19.7)	
Age	60-86	Mean (SD) 66.54 (5.97)	Mean (SD) 67.90 (5.16)	0.110b	Mean (SD) 66.98 (5.07)	Mean (SD) 67.65 (5.87)	0.638b	Mean (SD) 70.71 (7.10)	Mean (SD) 70.77 (8.97)	0.645b	Mean (SD) 67.86 (6.14)	Mean (SD) 68.80 (6.69)	0.544b

* P-value based on Chi-squared test; ** P-value base on Fisher's Exact test; a No statistics are computed because variable is a constant; b P-value based on Mann-Whitney U (age); Significant at 0.05 level.

There was observed a significant association between marital status and utilizing mammography test (p = 0.048). Married people had a higher rate of mammography test than others. Also, there was a statistically significant association between income and performing fasting blood sugar test (p = 0.028), blood lipid test (p = 0.024), and blood pressure test (p = 0.011). Having a chronic disease had a significant association with conducting fasting blood sugar test (P=0.011), blood lipid test (p = 0.047), and blood pressure test (p = 0.005). In this study, because the majority of people had health insurance, no significant association was found between insurance status and utilization of preventive care. There was no significant association between any of the demographic variables and conducting colonoscopy, fecal occult blood, and prostate tests (p > 0.05).

The results of multiple logistic regression analysis, provided in Table IV, showed that the elderly people with a chronic disease were more likely to perform a fasting blood sugar test and a blood pressure test than those without a chronic disease. Women were more likely than men to conduct a bone mineral density test. Retired people were more likely to utilize a Pap-smear test than unemployed people. Also, having middle and high income was related to a higher chance of conducting blood sugar, blood lipid, and blood pressure test in the elderly (compared to people with low income).

Discussions

The present study investigated the rate of utilization of preventive care services, and its associated socio-demographic factors among the Iranian elderly.

The findings of the study related to the utilization of preventive care services among the elderly referred to comprehensive health centers in East Guilan showed that blood pressure test (96.9%), blood lipid (88.8%), and blood sugar (87.5%) test were the most common types of utilized preventive care services, while colonoscopy (17%), fecal occult blood test (29.4%) and Pap-smear test (37.8%) were the least common types of utilized preventive care services among the elderly participated in this research.

In a study conducted by Peng et al. [11] in Taiwan, the utilization rate of the blood pressure test, fasting blood sugar test before a meal, and flu vaccine (flu shot) were over 50%. However, the utilization rates for most of the disease-specific preventive care services (such as mammography, colonoscopy, and fecal occult blood test) were reported less than 20%. In our study, the utilization rates of most cancers screening tests were reported as less than 50%.

In a study conducted in Belgium by Hoeck et al. [9] 63.1% of the elderly participants had measured their blood lipid and 55.3% of them had measured their blood sugar in the past, which were lower than those of present study.

Tab. IV. Result of logistic regression regarding socio-demographic factors associated with utilization of preventive services of research participants.

	Fasting blood sugar			Blood lipid test			Blood pressure			Bone density test			Pap-smear test		
	b	OR (95% CI)	Sig	b	OR (95% CI)	Sig	b	OR (95% CI)	Sig	b	OR (95% CI)	Sig	b	OR (95% CI)	sig
Income															
Low*															
Middle	2.11	8.3(1.93- 35.68)	0.004	2.10	8.22(1.93-34.97)	0.004	20.19	587944035.033	0.996						
High	1.16	3.19(.91-11.14)	0.069	1.31	3.72(1.03-13.43)	0.044	3.79	44.24(2.226-879.542)	0.013						
Disease															
No*															
Yes	1.35	3.88(1.12-13.46)	0.32	1.15	3.16(0.89-11.26)	0.075	4.76	116.828(6.03-2263.094)	0.002						
Age	0.058	1.06 (.959-1.172)	0.255	.070	1.07(.966-1.190)	0.188									
Gender										1.82	6.18(2.878-13.279)	0.001			
Occupation															
Unemployed*															
Employed													1.37	3.97(0.609-25.870)	0.149
Retired													1.16	3.21(1.306-7.913)	0.011

Dependent variable, preventive services, was dichotomized as no = 0, yes = 1; CI: confidence interval; OR: odds ratio; Significant at 0.05 level.

Raisi et al. [19] found that only 23.2% of elderly women have had a mammogram test in the last two years. Also, the utilization rate of the PSA test among men for prostate cancer screening in the past year was only 30%, and only 19% of the participant had utilized a fecal occult blood test in the past year for colorectal cancer screening. Compared to the Raisi study, our result showed higher values for all tests.

The rate of utilization of preventive care services varies across countries around the world. A study conducted by Jusot et al. [20] in 14 European countries showed that the Netherlands (84.5%), Sweden (83.9%), and France (83.2%) had the highest mammography utilization rates among women aged 50 to 69 years, while Denmark (24.7%) and the United Kingdom (29.1%) had the lowest utilization rate of screening tests. Also, Australia (67%) and Switzerland (42.5%) had the highest utilization rate for the colorectal cancer screening test and Spain (11.9%) and Greece (10.8%) had the lowest utilization rate for colonoscopy.

The differences observed between the results of the present study and other studies can be due to the factors affecting the use of preventive care services such as awareness, insurance coverage, having a history of a disease, the health concerns and sensitivities, different health systems across countries, cultural differences and socio-economic status of participants.

Bivariate analysis revealed, several demographic characteristics (i.e. age, income, occupational status, marital status, education, disease and gender) were found to be significantly associated with some preventive care. Also, multivariate analysis showed that among the significant variables in bivariate analysis, only income, underlying disease, gender and occupation status significantly associated with some preventive care.

A study in China found that gender, age, occupation and level of education, income, health insurance, history of high blood pressure, and diabetes had statistically significant effects on people's demand for preventive care services [21]. This was consistent with the results of our study in some influential factors.

The results of a study on rural Indonesian elderly showed that the elderly who suffered from a chronic disease utilized more preventive examinations compared with the elderly without a chronic disease [22]. Peng et al. [11] also showed that the presence of a chronic disease was associated with the utilization of most of the preventive care services (except mammography and Pap-smear). In the present study, the utilization rate of preventive care services was higher among people with an underlying disease, nonetheless, only the association of blood sugar, blood lipid, and blood pressure tests was statistically significant. Also, regression analysis indicated a greater chance of performing fasting blood sugar test and blood pressure test among elderly patients. It can be said that people with chronic diseases such as heart disease and diabetes are more likely to visit a doctor and they are recommended by doctors to utilize preventive care services [8].

In the present study, the income levels of most participants, who conducted blood sugar, blood lipid, and blood pressure tests, were moderate to high. Income differences are likely to contribute to the gap in accepting preventive care services. The results of a study in Saudi Arabia showed that the income level of people who utilized preventive care services was higher than those who did not [23]. People with higher income levels may also use private health care services or supplemental health insurance, which helps them have an easy access to health care services [24, 25].

A study conducted in Ghana indicated an association between income and self-control of blood pressure. The researchers reported that this may be due to the fact that high-income people could provide blood pressure monitors and therefore be able to control their blood pressure at home without any problems compared to low-income people [26].

The results of a study conducted by Vaidya et al. [13] indicated that women controlled their blood pressure and blood lipid more than men. Despite the fact that the proportion of women who utilized preventive care services was higher than men in the present study, this difference between the two genders was only significant in the utilization of the bone mineral density test. Moreover, in the study of Jafari et al. [27] the adherence rate to the bone mineral density test in women was 1.5 times that of men, which was similar to the results of the present study. Because osteoporosis is common in women of menopausal age, there is a possibility that men may consider this test specific to postmenopausal women and be less inclined to do it. Nevertheless, in general, less utilization of preventive care services in men reinforces the view that most men do not attend regular health examinations and are less likely to visit a doctor, indicating a missed opportunity to discuss preventive care in this gender [13, 28, 29].

In the present study, married women had a greater rate of mammography than unmarried women, and retired women had a greater rate of mammography than employed women and housewives. These results were consistent with the findings of Rakowski et al. [30] and Baljani et al. [16]. The greater rate of mammography among married women can be due to emotional and informational support from the family, especially the spouse [31] which can be an important factor in performing a variety of cancer screenings, including mammography. In terms of occupation status, we found that there was an association between occupation and conducting a Pap-smear test. Due to social interactions, retired women appeared to be more aware of the advantages of preventive measures including Pap-smear. In the study of Mupepi et al. [32] it has been reported that financially independent women were more likely to have access to cervical screening (a Pap-smear test) tests than women who were dependent on their husbands. This was consistent with the present study. In the study of Bahrami et al. [33] in Sanandaj city, the employment status of women was reported as one of the most important factors affecting the utilization of the Pap-smear test.

Peng et al. [11] showed that having a high school diploma was associated with more utilization of most of the preventive care services which were consistent with the results of the present study. Our findings showed that the education level of more than half of the participants, who utilized mammography, was high school and higher. A similar study found that there was a positive association between education level and some health-related behaviors, including participation in screening [34]. This is because educated people may have access to better resources and information, so they will become more aware of health and behavioral issues to improve their health [35]. Moreover, higher education may also influence preventive care through better occupation and access to care [36].

In a study conducted by Peng et al. [11] aging was shown to increase the likelihood of conducting blood sugar and Pap-smear tests. In the present study, based on the results of bivariate analysis, people who had their blood sugar and blood lipid tests were older than those who did not. Also, in our study, younger people had a higher utilization rate of Pap-smear test, mammography, and colonoscopy. This was consistent with the results of Simon et al. [37] that showed a negative association between age and conducting Pap-smear test and mammography. However, in our study, the difference between the two age groups was not significant. This can be attributed to the reluctance of some elder people of higher ages to be aware of diseases such as breast and intestinal cancer. Also, Richard et al. study showed that age was significantly associated with utilization of preventive care services. Older ages were associated with receiving more flu shots, while having a younger age was associated with utilization of more Pap-smear, mammography, and dental services [38].

Limitations of the study included self-reported answering to the questionnaire, and conducting virtual interviews, which were mostly conducted not in person due to the pandemic of COVID19 and lack of access to the elderly, which can reduce the accuracy of the results of this study to some extent. Also, the present study was conducted in the elderly group (people 60 years and older), so the findings cannot be generalized to other age groups.

Conclusions

Based on our findings, the utilization rates of screening test for most cancers, including gastrointestinal cancers, were low. Also, income was among the most important predictors for conducting blood sugar and blood lipid tests as well as controlling blood pressure. Moreover, having an underlying disease is one of the most important predictors of conducting blood sugar and blood pressure tests; gender was the most important predictor of a bone mineral density test, and occupation was one of the most important predictors of performing Pap-smear in the elderly participants. According to the results of the present study, developing policies and strategies aiming

to encourage the elderly population regarding adopting preventive care and making preventive care free for the elderly are recommended in order to increase the utilization rate of preventive care services. Also, further research is needed to explore additional factors that may influence preventive care utilization.

Ethics consideration

The present research was approved by the Ethics Committee of Guilan University of Medical Sciences (Ethics Code: IR.GUMS.REC.1399.626).

Consent to participate

Verbal informed consent was obtained from all participants.

Conflict of interest statement

The authors declared no conflict of interest.

Authors' contributions

RM: was involved in conceptualizing, generating of the project, data collection, and also drafting the manuscript; FB: was involved in conceptualizing, generating of the project, data analyses, and also drafted the manuscript; PP: assisted with the conceptualization of the project; BGH: assisted with the data analyses. All authors read drafts of the manuscript and provided comments.

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Ethics and humanization of care: Reflections in the teaching of French institutional psychotherapy experience

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Keywords

Institutional psychotherapy • Therapeutic process • Role-based interaction • Rehabilitation • Dignity • Individuality

Summary

French institutional psychotherapy, developed by Jean Oury and his team at the Clinic de la Borde, has played a significant role in the evolution of psychotherapeutic practice, highlighting the importance of considering the institutional context as a determining factor in understanding and treating mental disorders. This innovative approach, based on recognition of asylums' pathogenic effects, has placed particular emphasis on the humanisation of treatment and the application of bioethical principles within psychiatric institutions. This article aims to investigate the key elements of French institutional psychotherapy, analysing its relationship with bioethics and its contribution to the humanisation of care.

Introduction

In reflecting on the relationship between bioethics and psychiatry, we believe that special attention should be given to a careful examination of the French experience of "institutional psychotherapy" [1,2]. It is important to understand what has been and continues to be at stake for the practice of psychiatry, and how this current of thought and medical practice represents an alternative to the antipsychiatry movement, while still addressing the same fundamental bioethical need for the humanization of institutions [3,4].

Institutional psychotherapy is closely linked to psychiatrists François Tosquelles and Jean Oury and their approach based on the undeniable principle that mental illness should never be a reason to deny a person their humanity and fundamental rights [5].

In this context, we focus on examining the key aspects of care paradigm proposed which led to the creation of the psychiatric clinic La Borde, an inspiring model for institutional psychotherapy in France firmly grounded in the respect for the dignity and rights of people with mental disorders. Our aim is to highlight the relevant ethical aspects not only for contemporary psychiatry but also for a care model that can be applied in other contexts as well. This model focuses not only on addressing the biological factors but also on promoting the person's development and whole relational context.

Indeed, institutional psychotherapy is simultaneously a European form of "pragmaticism" and Peircean hermeneutics, as well as a well-established realm of experimentation that values the ethical dimension of caring for the most vulnerable individuals [6]. It involves practicing a psychiatry founded on an original conception of cooperation between medical personnel and patients within the institution. This approach not only emphasizes the effectiveness of treatment but also prioritizes ethical principles, such as respect for patient autonomy, dignity, the promotion of humanistic values in the therapeutic process and the affirmation of health democracy [7]. The care is conceived as a collaborative process, in which patients and healthcare professionals work together to achieve psychological well-being, confirming the subjectivity and the same dignity of all participants in the therapeutic process, preventing the possibility of the participants transitioning into rigid role-playing positions of classical hierarchy therapy [8,9]. True ethical sensitivity manifests itself in those moments of life that involve acknowledging the humanity of others and us.

The most emblematic maxim of institutional psychotherapy is based on a postulate that the ongoing clinical experience at La Borde confirms in its results and practices: the institution is not a place, it is not the physical structure that host patients, but the structured and dynamic articulation of different constitutive functions, which is the essential and primary factor in the care of the mentally ill. From this postulate derives the famous maxim: "To promote the mental health of patients, we need to treat the institution in which they are welcomed and cared for".

We will attempt to demonstrate, through a brief overview of its history and an analysis of the theoretical and practical aspects of the clinical experience at La Borde, how institutional psychotherapy can today offer an interesting proposal for psychiatry. Embracing the undeniable ethical need, promoted by Basaglia, for the

humanization of psychiatric care, the French therapeutic approach seeks to identify the conditions under which psychiatric institutions can become, as the experience of La Borde teaches us, essential factors for effective and respectful treatment of individuals, rather than merely abolishing them [10].

Brief Historical Overview

The clinical experience practiced at La Borde, based on the fundamental principle of free circulation, in complete contrast to the old asylums or some of the current psychiatric hospitals operating in Europe, serves as the premise for any reflection on institutional psychotherapy.

Jean Oury first met François Tosquelles at the clinic of Saint-Alban, where the Catalan psychiatrist proposed a model of a "healing" institution in which patients were familiar with precise rules of cooperation and organization but faced no restrictions on their free movement within the facility. As a young psychiatric intern at Saint-Alban, Oury was immediately captivated by Tosquelles' style, appreciating not only his innovative clinical approach but also the richness of the philosophical thinking that inspired it. Oury, along with Lacanian psychoanalysis, would make philosophy a fundamental ally of psychiatry [11]. Emmanuelle Rozier writes: "I discovered La Borde clinic in 2002 when a friend invited me to listen to Jean Oury in the room called the 'Rotonde,' a hexagonal room where meetings are held. Although I only partially understood what was being said in an ambiance where followers, Parisian psychoanalysts, patients, dogs, and cats of all kinds were gathered. I was struck by his way of thinking about daily life, about the *praxis*. Oury quoted philosophers, psychoanalysts, and writers to articulate life within the clinic, the question of psychosis, and his psychiatric practice" [12]. These few lines immediately introduce us to a unique context where, even today, nine years after Oury's death, this fruitful encounter between various knowledge and practices makes La Borde a singular and extremely interesting place to explore and understand.

The encounter with Tosquelles was what led the young fourth-year medical student, Jean Oury, to decide on psychiatry. A series of conferences took place in 1947 at Saint-Alban, attended by Tosquelles, Henry Ey, Ajuriaguerra and other prominent figures of the time. It was a lecture by Lacan in May of that same year that directed Oury towards psychiatry. After completing two years of internship under Tosquelles' guidance, Oury was appointed head of a "dead clinic" with a capacity of only 12 beds in Saumery, near Blois. In 1949, Oury accepted the position, hoping to transfer the epistemology and clinical approach of institutional psychotherapy to this location. However, after four years of attempts to create workshops and living spaces suitable for his conception of psychiatry in Saumery, Oury informed the Medical Board of his decision to leave the clinic with all the patients.

On April 3, 1953, the small community led by Oury, who had temporarily left some patients behind in Saumery, later to join him, settled in Château de la Borde, located in the municipality of Cour-Cheverny. The property was purchased with heavily mortgaged loans, thus marking the beginning of the most significant experience of institutional psychotherapy.

La Borde's uniqueness

The application of bioethical principles is a fundamental aspect of French institutional psychotherapy [13]. Within the context of institutional psychotherapy, ethics intertwines with the therapeutic approach itself.

We aim to present the fundamental aspects of this reality that has inspired and could still inspire the practice of institutional psychotherapy in any caring place, not only psychiatric, in France or in another European Country. In presenting the fundamental aspects of this approach, which is still capable of playing a significant role in the evolution of institutional psychotherapeutic practice, founded on the ethical principles of humanizing care, it seems useful to indicate the necessary theoretical principles for the creation of spaces, functions, and clinical modalities representing the original character of the experience.

THE INSTITUTION AS AN INSTRUMENT OF CARE

What exactly does it mean for an organization to become not just the place where one is cared for, but the primary factor of care? A first and central element is the idea of a structured collective functioning harmoniously like a living organism [14]. Following the teachings of Tosquelles, Jean Oury entrusts all care daily activities to this integrated and collective system. The underlying guiding idea is that in order to ensure a freedom that respects human dignity, it is necessary to organize life, establish rhythms and rules of functioning that are shared and for which everyone is directly responsible. This type of organization resembles the physiology of a human organism and requires absolute fairness in the types of roles and tasks it entails in order to sustain itself and operate effectively. Therefore, if it is true that the collective is at the core of this type of institution, serving as the guarantor of its vitality, it is necessary to grasp its characteristics in detail so as not to turn its role into a utopia.

Before even understanding the functioning of this structured and structuring entity, it is nonetheless necessary to delve into the role that each individual can and is called upon to play. A fundamental principle, with significant ethical implications and concrete consequences, is what can be defined as the "diffusion of the caregiving action". According to institutional psychotherapy, every person who acts within the collective has, in addition to their specific skills and functions, a caregiving action simply by entering into cooperative relationships for the construction and the management of a shared living space. Jean Oury used to say that the true "categorical" difference at La Borde was between "those who paid and those who were paid",

while the caregiving function was exercised by everyone. This statement captures the essence of the approach at La Borde, emphasizing that the act of providing care transcends monetary transactions and is a responsibility shared by all individuals within the institution.

In order for this to be true, the collective needs structured and structuring spaces and must base its practice on the idea that an institution has the fundamental vocation to provide care, recreate a sense for each individual within a shared organizational and a geographic perimeter [15]. This containing and structuring function is essential for psychotic individuals, particularly for those with schizophrenia, who experience the tragic phenomenon of the "fragmented body" [16]. In a context where they may find themselves attending a conference, cooking together with a nurse, or even with their psychiatrist, within a logic where the essence of their shared humanity is made visible through the organic interplay of different community roles, performed in turn by anyone, something of the splitting – typical of this disorder as Bleuer identified- is recomposed or at least contained.

By creating these structured spaces, the collective can foster an environment where individuals are welcomed and supported, allowing them to cultivate a sense of belonging and meaning to be cultivated within the institution. This shared sense of purpose and belonging within a common framework is essential for the collective to fulfill its fundamental role of providing care.

CARING RATHER THAN HEALING: THE CONCEPT OF NORMOPATHY

The fundamental postulate that supports the model proposed by Oury is therefore that the institution cares, without worrying about healing. Any potential healing, envisioned as the ultimate possible horizon, does not constitute the goal of collective efforts. The widespread action of care is the true objective that guides the movement of staff and patients, considering all of them as agents of care for one another. In the characterization of this care model, the neologism, coined by Jean Oury, "normopathy", is emblematic as it establishes a true epistemology in addition to its undeniable impact. Beyond psychosis, which in its various forms alienates the individuals and confines them to a space of rupture and exclusion from the realm of shared meaning, there would not be a presumed "normality", but rather another fundamental human experience that suffers from the confusion between the norm and normalization. It is necessary to reference Georges Canguilhem, a prominent French physician and epistemologist, who highlighted in his major work, "The Normal and the Pathological" how every situation of anomaly, whether in the biological or psychosocial realm, always leads, albeit subjectively, to another operation of structuring normativity, reorganizing around different logics of functioning [17].

In particular, both in the case of physical health and in the case of mental health, Canguilhem argued that illness and the mental disorder represent a sort of persistent anomaly that arises within an equilibrium in which the organism or system regulates pathological processes based on a certain normativity, a series of responses that

ensure that the specific context remains physiologically healthy [18,19]. If the anomaly persists and disrupts the harmonization of vital processes, it produces illness, which in turn tends to regenerate another norm that reorganizes the system around a different equilibrium. According to Canguilhem, a sick person is someone who is compelled by the anomaly to construct a new normativity. Nothing and no one truly escape from normality in the sense of a permanent rupture: every living system tends to restore the organic harmony of physiological processes, whether in the strictly biological realm or in the psychological and social domains.

In this sense, institutional psychotherapy asserts that psychosis, ordinary madness in its various forms, concerns each one of us as part of the harmonious yet complex fabric of social bonds that support "living-with" others. Intrapsychic anomaly has an immediate resonance within the interpsychic domain, with the consequence that the entire system of psychosocial interaction, just as in a living organism, is mobilized to generate a new normativity around which life is reconfigured as possible. Quoting Jean Furtos, Paul Jacques writes: "Psychic precariousness corresponds to psychic vulnerability in the face of the world's wavering and the difficulties of recognizing oneself as worthy of existence within a particular human group (Furtos 2001: 3). Psychic precariousness is social death [20]". Because of this awareness, at La Borde, the main agent of care is the structuring function of cooperation within the institution.

THE COOPERATION AND ITS SPACES: ARE IT REALLY POSSIBLE TO SHARE DAILY LIFE WITH PSYCHOSIS?

As Joseph and Proust affirm the fundamental question is: "How can we describe and understand the emergence of psychosis – and its most common form, schizophrenia – both as a psychological phenomenon and a social event? In its mode of manifestation, psychiatric disorder appears as a rupture of common evidence, a disturbance of shared intelligence" [21]. For this reason, cooperation appears as the primary tool to restore and harmonize shared intelligence within a care institution. The first attention to be given is to the spaces where a cooperative dynamic can take place. In other words, real and symbolic common places are needed where sharing can materialize through everyday words and gestures.

The physical spaces at La Borde are divided into five sectors, where everyone (psychiatrist, patient, "moniteur", French word for "facilitator/caretaker", administrative staff, or guest) can move freely. This means that in each of these sectors, it is possible to interact and cooperate in order to manage the daily life of everyone involved.

But the main place of cooperation remains "The Club".

"The Club is everywhere" is the message conveyed to the interns who, in great numbers, request to spend a period of internship at the clinic each year. This expression was coined by Jean Oury himself, who liked to make the philosophy of the caring institution transparent in this way. Emmanuelle Rozier writes, "It is no longer a question of being treated or treating, but first and foremost, 'members of a club.' As for the purpose of this group of people,

it should be noted that the club manages around forty workshops (ateliers) ranging from the more traditional ones, such as painting or ceramics, to horse riding, the bar, and even workshops related to the management of the club itself, such as accounting or 'the daily sheet'" [22].

This space of cooperation, in which, for example, the daily sheet indicates for each person (operator or patient) their role and contribution in various activities (clinical, social and cultural animation, management and administration), obviously requires special attention to communication, not just information. Mere information is not sufficient, but it is essential for the organization to train individuals in those modes of contribution through which communication serves not only to transmit a message but also ensures the quality of relationships. Only a certain type of communication allows for the absence of any higher authority regulating interactions: every effort to harmonize and manage daily affairs is based on equality among all participants.

But if "the madman" is, by definition, as Joseph and Proust state, "the one who makes us lose common sense", what kind of communication can help mitigate the effects of this loss of shared meaning in the relationship with psychotic individuals? The British philosopher of language, Herbert Paul Grice, defines them as "conversational maxims" [23]. There are four of them, and we can briefly summarize them, paying particular attention to their application even with individuals who deviate from the norms of shared common sense.

Maxim of Quantity: Be as informative as necessary but not more than necessary. The focus is on providing a message that appears sufficient in terms of contextual information and the content of the message itself, while being free from unnecessary redundancies or additions that often reflect a desire for acceptance from the other party rather than a goal of clarity.

Maxim of Quality: Be truthful and provide information that is supported by evidence. Avoid saying things that are false or lacking evidence.

It is not about assuming an objective truth, but rather aiming to state nothing that is not actually accurate or in some way "verifiable" in terms of its accuracy. The statement of "not knowing" can be a truthful assertion, just as much as knowing things precisely; the truthfulness of a statement cannot depend on a belief but rather on knowledge, which, like all knowledge, is subject to evolution in the progress of understanding. A statement of believing that things are a certain way without being able to verify it can also be considered truthful.

Maxim of Relation: Be relevant in your communication. Ensure that your statements are connected to the ongoing conversation and contribute to the topic at hand. It involves seeking the closest connection of our communication with what we want to express. Relevance implies a semantic and contextual proximity that presupposes truthfulness but adds a character of a close connection to the core of the message, enabling communication to have greater effectiveness.

Maxim of Manner: It binds us to the ethical obligation of taking care of how we communicate. Clarity, non-ambiguity, and correspondence between intention and message are at stake here, making our speech fluid, less repetitive, and devoid of aggression. It emphasizes the importance of conveying our message in a clear and respectful manner, ensuring that our words are easily understood and free from unnecessary hostility or confusion.

Applying these conversational maxims can help foster effective communication even with individuals who deviate from the norms of shared common sense, such as psychotic individuals.

In addition to these maxims that can guide communication, it is also necessary to acquire a good understanding of the difference between the "subjective" and "objective" dimensions, particularly when dealing with individuals who, even if all the conversational maxims are respected, show an inability to share a minimum common understanding. In such cases, it is important to prioritize what can maintain a fluid and protected relationship. If a person has lost the ability to connect to a harmonious intersubjective dimension and demonstrates a primary need to be recognized as a subject with their own sense and intentionality, it becomes futile to insist on a concept, no matter how truthful it may be, if it does not resonate with that person's experience.

In his work "Parler avec les fous" (Speaking with Mad ones), Henri Grivois [24], a renowned emergency psychiatrist, outlines four points that guide his clinical approach:

Bringing the patient back to a state of centeredness by using paraphrases and circumventing the obstacle on which he/she stumbles instead of confronting it directly.

Constantly returning to the relational aspect of the situation, seeking personal contact with the patient.

Acting as a barrier to the flow of delusional interpretations in order to protect the patient from him/herself.

Becoming the primary therapeutic factor in the therapeutic relationship.

The objective is not to make the person give up his/her delusional and invasive belief, but "rather to create a pathway through it towards bodily experience, which is the only thing that allows the dynamic and automatic connection with others and bring the patient back to their starting point" [24]. Grivois emphasizes the importance of establishing a therapeutic relationship based on understanding, empathy, and guiding patients towards reconnecting with their bodily experience [25].

What is the lesson of institutional psychotherapy?

From what has been described, it emerges that institutional psychotherapy, primarily developed in the psychiatric field, carries a vision of care that places respect for the person at its core, acknowledging their uniqueness and singularity. In this sense, it shows a possible path towards humanizing psychiatry.

Two fundamental elements of institutional psychotherapy allow us to draw a crucial and instructive lesson for "sector psychiatry" (outside hospital's walls) in the various countries where it is practiced.

The first is the concept of multi-referential transference. Jean Oury talked about dissociated transference as a typical characteristic resulting from the same schizophrenic dissociation (Bleuler's concept of *spaltung*). The notion of multi-referential transference is referable to Tosquelles. When a patient arrives at the emergency room in acute psychotic decompensation, He/she interacts with different individuals, each engaging in a different relational dynamic. For example, the patient may spontaneously share important personal information with the nurse, while being guarded and suspicious with the psychiatrist, and establishing direct trust with the staff member who brings them meals. Tosquelles defines the patient's transfer modality as "multi-referential," as three different people have encountered the patient, and each one has shared a distinctly different experience with him/her. However, all three aspects are important; these three "referents" have been invested in different or even antagonistic ways by the patient, and they all serve as "receptacles" for the patient's transfer, representing their institution. It is not a matter of determining who is right, but rather of seeking how to bring together these three experiences to come as close as possible to the patient's lived experience.

Tosquelles introduced the concept of the "transference constellation meeting and, in doing so, gave substance to the institution for the patient. Ultimately, it involves creating a specific institution for each patient" [26]. This latter statement, which constitutes the heart of the philosophy of institutional psychotherapy, outlines an important guiding principle in clinical practice through the idea of multi-referential transference and its organization into a constellation.

The second central aspect of the philosophy and clinical thinking underlying institutional psychotherapy is "the triad of functions": "phoric", "semaphoric," and "metaphoric." Entirely based on the hermeneutic triad of Charles Sanders Peirce's theory of interpretation [27] it reflects the three logical-phenomenological scansions of "primeness": the emergence of symptomatic manifestations as potential signs of a different meaning that the therapeutic relationship welcomes; "secondness": the expression of more precise signs whose potential for significance is activated through careful and precise listening by the caring person within the transferential constellation involving doctors, nurses, therapists, and staff members; and "thirdness": the symbolic interpretation of signs within a broader semantic context which goes beyond the singularity of the patient and allows a diagnosis and a tailored caring intervention. Once again, we rely on the words of Pierre Delion to better define the three typical functions of institutional psychotherapy in the treatment of autistic children.

First of all, the phoric function (primeness), derived from the Greek word "forein," meaning to carry: "The caregivers welcome and carry the autistic child who arrives at the day center into their psychic attention. In doing so, they make their own psychic apparatus available to the child, receiving the signs that translate their anxieties, reliefs, and questions." Immediately after, "by being available to the child, the caregivers perform a semaphoric function (secondness) [...] carrying signs: they are the receptacles

of the signs of the child's psychic suffering," even though initially they may not be able to understand the subjective meaning to which these signs refer in the child's semantic and existential universe. It is only through the gathering of the constellation, in the sharing of transference and counter-transference experiences among different caregivers, that a sign (the appearance of inexplicable archaic anxiety) will be interpreted and give rise to meaning (seeing different people arriving at an unusual time) thanks to the metaphorical function operating within the constellation. In this example, something sameness (the arrival of different people at an unusual time) also evokes the exact opposite for the child: the irruption of an ungovernable, unpredictable time. This ambivalent experience, simultaneously recurring and unpredictable, triggered in the actual case of the child the expression of primal anxiety which would be nothing but a pure, undefined anomaly without the intervention of the metaphorical function by the transference constellation" [26].

Conclusions

The analysis of theoretical and clinical aspects of institutional psychotherapy shows how this therapeutic approach, firmly founded in the values of acceptance, respect for the dignity of the most vulnerable individuals and the social responsibility of all those involved in treatment, is characterized by its humanistic philosophy and strong ethical connotation. In fact, it aims to build a therapeutic environment that not only aims to alleviate the patient's psychic suffering, but also to promote a broader social change, fostering inclusion and patients' active cooperation in the construction of their care pathway and in the restoration of their own identity.

Based on the acknowledgement of the uniqueness of each individual and his/her own history, this person-centered approach affirms that disease cannot be objectively understood apart from how the experience of illness is experienced by the patients within their specific history and culture.

The healthcare workers' focus is not only on symptom reduction, but also on emotional support, stress management, and the development of patient's adaptive abilities. This allows valuable support in achieving a sense of satisfaction and personal fulfillment, not only from a clinical perspective but also across various dimensions of their daily life.

By respecting each person, seeking active collaboration, emphasizing the quality of the therapeutic relationship, recognizing the importance of the social and community dimension, and promoting well-being and quality of life, institutional psychotherapy offers a humanistic and respectful approach to psychiatric care.

It also represents a real possibility of positively influencing the clinical theory and practice, even in other therapeutic domains.

For these reasons, it is crucial to adequately train healthcare professionals so that they can acquire a set of skills that include attentive listening and empathetic

interaction. This should be done with a renewed perspective that emphasizes the human dimension in welcoming, supporting and caring patients. It is worth noting in this context the recent Italian law on informed consent and advance directives that, in line with what has already been established by the medical code of ethics, has determined that the time dedicated to communication is a proper "time of care" [28,29].

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The authors declare no conflict of interest.

Authors' contributions

All authors conceived the study and contributed to the preparation of the manuscript related to their sections and approved the final version to be submitted.

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Measles: a new danger for Ukraine's children! The need for an effective and timely vaccination prevention campaign for an insidious disease that comes from afar

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Summary

Background. *Measles, a highly contagious and dangerous disease that can cause disability or even death, remains endemic in Ukraine. This is a serious public health problem that absolutely needs to be monitored. Indeed, in the years 2017-2019, Ukraine was hit by a major measles epidemic, which caused serious problems for the population. The numerous efforts to contain the spread of measles in the country are now waning in the face of a devastating war, which has already lasted for over a year, and the COVID-19 pandemic, which has further complicated the general situation.*
Method. *In this paper, the authors highlight a very serious public health problem and invoke the immediate implementation of an effective vaccination policy.*
Discussion. *The percentages of measles vaccination coverage in Ukraine have decreased drastically since the beginning of the conflict (which began on February 24, 2022), and this is a source of*

concern regarding the possibility of a new major measles epidemic. Indeed, a measles epidemic at this time would have frightening consequences, given the conditions in which the Ukrainian population is now living. The United Nations estimates that at least 6 million people have been displaced within Ukraine as a result of the conflict, and this internal mass exodus has significantly affected vaccination coverage and adherence to vaccination schedules, despite the efforts of the Ukrainian health authorities.
Conclusion. *The ministry of health has prioritized vaccination programs with the help of the World Health Organization (WHO) and UNICEF, which are ensuring the free supply and delivery of vaccines through the deployment of mobile vaccination teams, even in areas where health facilities are not accessible. The main objective is to vaccinate as many people as possible in order to avoid a new epidemic, which could spread to the whole of Ukraine and also to other countries.*

Introduction

The war that has been devastating Ukraine for over a year has not only caused death and destruction; it has also undermined the possibility to provide acceptable healthcare for the civilian population.

Ukraine is currently facing a double challenge with a severe and significant high risk of measles outbreaks.

On the one hand, the country struggles with low immunization coverage, leaving a significant portion of the population susceptible to the highly contagious measles virus.

On the other hand, the ongoing war scenario certainly complicates efforts to contain the disease, promoting the rapid spread of measles.

The most fragile and vulnerable subjects are children. Indeed, the thousands of Ukrainian children who have fled their homes cannot receive vital vaccines to protect them against diseases such as poliomyelitis [1], diphtheria, measles and other diseases, which threaten their lives as much as the bombs that continue to fall on their cities [2].

In March 2023, UNICEF delivered 35,200 doses of combined measles, mumps and rubella vaccines (MMR) free of charge to Ukrainian authorities as humanitarian aid

to support the National Immunization Program [3] and, in particular, to provide catch-up vaccination for children who have missed a dose in the vaccination schedule. The shipment of these vaccines has been brought forward, owing to reports of some confirmed cases of measles in Ukraine, the aim being to avoid the risk of an epidemic of one of the most contagious infectious diseases in the world, whose cases have returned to grow also in Europe and in Italy itself [4, 5]. In addition, in early April, UNICEF provided 543,000 doses of oral polio vaccine and 110,160 doses of inactivated polio vaccine, and by the end of April, 6 large, refrigerated vehicles to transport vaccines [3].

"Measles activity continues to be low in the EU/EEA, but outbreaks have started to occur, *e.g.* in Austria and Slovakia. In January 2023, a total of nine confirmed cases of measles were reported to TESSy by six EU/EEA countries. On a global scale, cases and outbreaks have been reported in England (UK), Ukraine and India, and are being reported in different WHO Regions (AFRO, PAHO), including the Democratic Republic of the Congo, Republic of Tanzania, South Africa, Canada, and the United States" [6].

Fig. 1. A child with the classic day-4 rash with measles (Public domain image)

Measles in Ukraine: a primed bomb

Measles is an extremely serious and highly contagious disease caused by a virus of the paramyxovirus family; it is normally transmitted through direct contact and through the air.

The crowded living conditions and population displacement resulting from the conflict create an ideal environment for the virus to spread. Insufficient and poor immunization coverage, coupled with a high influx of internally displaced persons and limited access to healthcare, increase the likelihood of measles outbreaks, especially among vulnerable populations such as children, the elderly, and those with weakened immune system. Measles outbreaks can have severe consequences, including complications such as pneumonia, encephalitis, and even death.

As has happened in the past for other epidemic diseases [7, 8], as a result of vaccination campaigns, the number of deaths from measles has declined markedly over the years. Before the introduction of the measles vaccine in 1963, exactly 60 years ago, measles epidemics occurred every 2 or 3 years, and the disease killed about 2.6 million children each year. "Even though a safe and cost-effective vaccine is available, in 2018 there were more than 140,000 measles deaths globally, mostly among children under the age of five" [9].

Measles is endemic in Ukraine, and two major outbreaks have occurred in the last decade. While 105 cases of measles were reported in 2015, and 102 in 2016, the number rose to 4,782 in 2017; the following year saw a surge up to 53,219 cases, and in 2019 the figure increased further, reaching 57,282 (Fig. 3) [10].

Moreover, between 2017 and 2019, more than 115,000

Fig. 2. Lithography of 1912 depicting the different arrangement of the rash in measles and scarlet fever (Private collection).
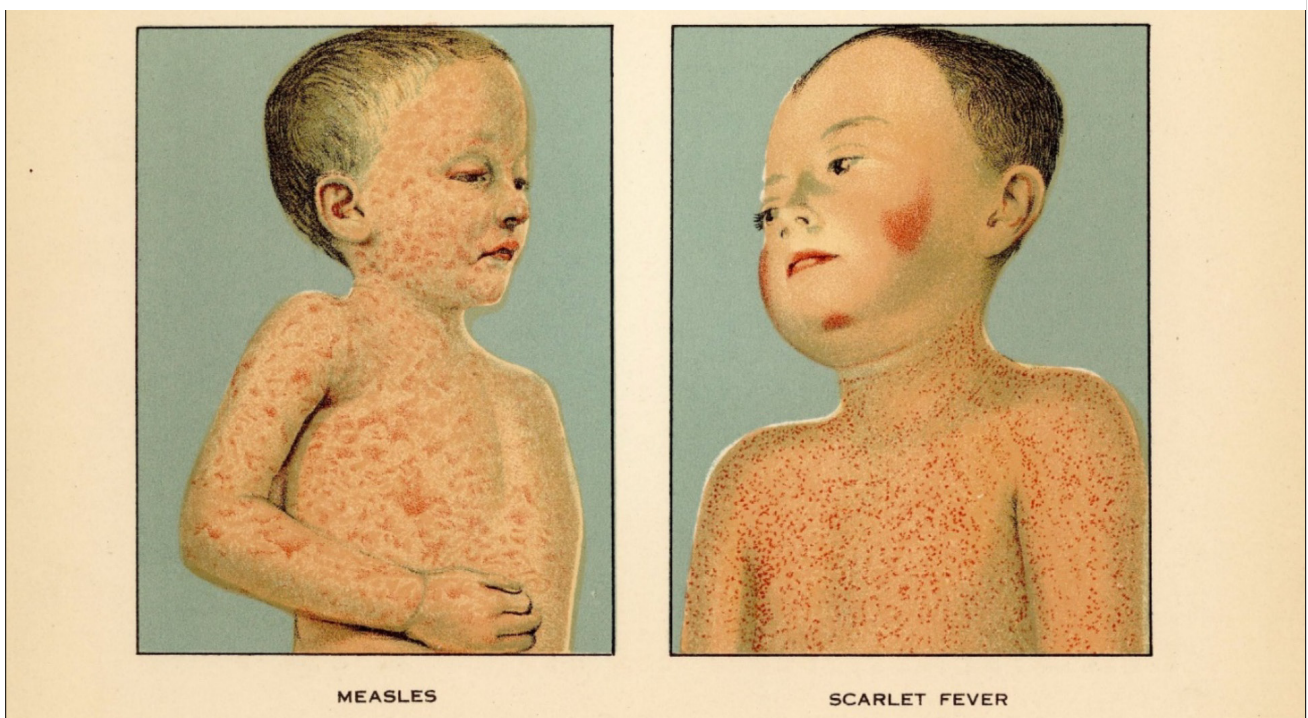
Fig. 3 Measles - Number of reported cases in Ukraine between 2015 and 2021 (Data from World Health Organization - The Global Health Observatory).

Measles - Number of reported cases in Ukraine between 2015 and 2021

people in Ukraine were infected and 41 died [11]. Most of the infections occurred in people who had not been vaccinated or who had not completed their course of vaccination.

This was one of Europe's largest outbreaks in the last 20 years [12]: Professor Andrii Loboda of the Department of Paediatrics at Sumy State University in Ukraine said that 65-67% of those affected were children and 33-35% were adults [13].

Given the current condition of the country and the current insufficient levels of routine vaccination, there is now a high risk that a new epidemic could occur, and this absolutely must be avoided. The consequences this time could be truly devastating for a population exhausted by war, cold, disease and without the possibility of proper treatment.

At the start of the 2017-19 outbreak, measles vaccination coverage in Ukraine was 42%, a figure that was not even half of what the WHO considers necessary for herd immunity (95%) [13]. Vaccination coverage against measles has significantly decreased during the period 2008-2016 from 96% to 45%. This was due partly to shortages in vaccine procurement and partly to widespread vaccine hesitancy [14, 15] on the part of the population and also some healthcare workers [16-18].

Thanks to the efforts of the Ukrainian health authorities, the vaccination coverage rate subsequently reached 88% in 2021. However, owing to the war, this rate fell back to 74% in 2022 [13].

This serious lack of immunization causes significant percentage of vulnerable population.

As a result, there are recurring waves and surges of measles cases in Ukraine, with potentially devastating effects. We also add that displacement, population movement and overcrowded living conditions in affected areas can increase the risks and possibilities of measles transmission.

It is therefore necessary to reschedule vaccinations according to a schedule that includes two doses administered at the age of 12 months and 4-6 years. This is a considerable commitment for a country at war and with health facilities that do not work and partly destroyed. Then we must consider that part of the population is displaced. The situation makes it even more difficult to organize vaccinations, also because there are no reliable data on the number of births in recent years due to COVID-19 pandemic and war. The last certain figure is related to 2019 with 308,817 births in the year compared to 581,114 deaths, with an annual variation of -0.60%, in line with the trend of the years 2017/2019 [19].

The protracted conflict in Ukraine will increase the risk of measles epidemics.

Conclusions and perspectives

The risk of measles epidemics in Ukraine is certainly increased due to low vaccine coverage and the ongoing war scenario. Urgent action is needed to control and fill gaps in immunization coverage in Ukraine and it is important to improve public perception by population, exchange of information, public awareness, and development of public health strategies. All these preventive actions can reduce risk of measles outbreaks. It is therefore necessary now to support Ukraine in the effort to vaccinate at least 95% of the population against measles; only in this way can we interrupt the transmission of the virus and prevent the return of major epidemics [20].

Moreover, it is equally essential to raise public awareness of the risks of this potentially deadly disease. Preventing the spread of measles in Ukraine is extremely important not only for the local population, already exhausted

by more than a year of war, but also for the world's population.

Indeed, in 2021 alone, as a result of COVID-19, wars and unstable political situations, in addition to the phenomenon of vaccine hesitancy, almost 40 million children in the world missed a dose of the measles vaccine: 25 million did not have the first dose and another 14.7 million missed the second dose.

Collaborative efforts between government agencies, healthcare providers, humanitarian organizations, and international partners are crucial to really fight this dual challenge and protect the population from the harmful consequences of measles epidemics.

On the global journey towards achieving and sustaining the elimination of measles, this is a setback that we absolutely cannot afford…! Nor must we forget that measles remains endemic in 18 countries (34%), as does rubella, while 16 countries are endemic for both diseases, one of which is Italy [21].

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The authors declare no conflict of interest.

Authors' contributions

DO and MM designed the study, conceived, and drafted the manuscript; the authors revised the manuscript, performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the paper for publication.

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INFECTIOUS DISEASES

Poc (Pox), a term for various infectious diseases in the history of public health and epidemiology: the dreaded *Smallpox*, the almost unknown *Alastrim* and the *Mpox*

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Summary

Introduction. *In 2022, the appearance of cases of Mpox outside the countries where the disease is endemic, and of some cases of human-to-human transmission, alerted the scientific community to a virus that is closely related to the smallpox virus. Mpox is a zoonosis and can be transmitted to humans. Following the eradication of smallpox in 1980 and the subsequent cessation of smallpox vaccination, it is emerging as the most important Orthopoxvirus in terms of public health impact.*
Methods. *In outlining the current situation of Mpox in the world, the authors frame the virus responsible within a broader reflection on the Orthopoxvirus family, focusing particular attention on the Variola virus, which formerly caused millions of deaths.*
Discussion. *Since Edward Jenner initiated the practice of vaccination, a progressive and careful vaccination campaign has led to the eradication not only of human smallpox but also of a minor form, called Alastrim, which was caused by the same virus. The mode of transmission of Mpox has been debated. At first, it seemed that the disease mainly, though not exclusively, affected men who had sex with other men. This conviction has been partially revised and the WHO recently changed the name of the disease from Monkeypox to Mpox, thereby alleviating the stigma involved.*
Conclusion. *The recent human cases of Mpox have prompted greater surveillance and research into the biology of MPXV and other closely related poxviruses. Studies have focused on the natural history of the virus, its transmission, pathogenesis, host interactions and evolution, and on the development of drugs and vaccines to prevent its spread.*

Background

In May 2022, the first cases of monkeypox (*Mpox*) were reported in countries where the disease is not endemic [1].
As of 5 June 2023, a total of 87,929 laboratory-confirmed cases of *Mpox* and 146 deaths have been reported to WHO. Since May 2022, a high percentage of these cases have been reported from countries without previously documented transmission of *Mpox*. It is the first time that cases and infections have been reported in countries without direct or immediate epidemiological links to areas of West or Central Africa [2].
The monkeypox virus is an *Orthopoxvirus* that causes a disease with symptoms similar to smallpox, although less severe. *Orthopoxvirus* is a genus of dsDNA viruses in the Poxviridae family that infect mammals.
Monkeypox virus (MPXV) is a double-stranded DNA virus. It is normally associated with rodents and occasionally spreads to humans. The emergence of cases in countries not normally affected by *Mpox* has brought to the attention of society a family of viruses which includes the terrible *Variola virus*, or smallpox virus, which killed millions of people for centuries [3].

Smallpox is an extremely contagious, severe infectious disease, with a historical fatality rate of around 30%. The disease is transmitted from person to person, as there are no other reservoirs in nature. It has been dreaded since ancient times, owing to both its high mortality and the fact that survivors were left with disfiguring marks all over their bodies.
Although there is evidence of smallpox dating back thousands of years, the timing of the appearance of the causative agent of the *Variola virus* and the way it evolved have caused quite a few controversies among scholars.
In 2016 Hendrik Poinar, a biologist specialized in ancient DNA has reconstructed the family tree of the *Variola virus* extracted from a 17th century Lithuanian mummy and established that the common ancestor appeared in modern historical times, between 1530 and 1645 [4].
Smallpox was eradicated in 1980, thanks to an intensive worldwide vaccination program.
Vaccination is a method of preventing smallpox, devised in 1796 by the English physician Edward Jenner (1749-1823) [5], who presented it in his book *The Origin of the Vaccine Inoculation* (1801) [6]. Having observed that people who had recovered from "*cowpox*" did not

contract "*smallpox*", Jenner deduced that the former disease could confer protection against the latter [7]. He began vaccinating healthy people by injecting material from a cowpox pustule. After developing the disease, the vaccinated person became immunized for both cowpox and human smallpox. This result was due to the similarity of the antigens of the two viruses: antibodies active against cowpox were also active against smallpox [8,9]. The smallpox vaccine was created by using viruses of the same species of *Orthopoxvirus*: *Cowpox virus* and *Vaccinia virus* (VACV), which do not cause human smallpox but elicits cross-immunity which protects the vaccinated individual against possible attack by the *Variola virus*.

Cowpox virus, *Vaccinia virus* and *Variola virus*, the cause of smallpox, are all closely related immunologically. For this reason, both VACV and CPXV determine immunity to smallpox.

VACV was the first animal virus to be purified and chemically analyzed. It was also the first virus to be genetically engineered, the recombinant viruses being utilized in vaccines against other infectious diseases" [10, 11].

Today, 200 years after the death of Edward Jenner, the world is still indebted to him for this fundamental discovery, which enabled smallpox to be eradicated and inspired the creation of vaccines against many other diseases.

Although the smallpox virus (*Variola virus*) has been eradicated worldwide, it is still preserved in some laboratories, and the possibility that it may be accidentally or deliberately reintroduced could have catastrophic consequences. In the event of biological attack, devastating smallpox epidemics could spread elsewhere but thankfully World Health Organization (WHO) and some countries like Italy have in their stocks important stash of vaccine.

There are 12 known *Orthopoxvirus* species, four of which can infect humans: *Variola virus* (VARV), *i.e.* the virus of human smallpox and *Alastrim*; *Monkeypox* (*Mpox*) *virus*, *Cowpox virus* and the *Vaccinia virus* used for smallpox vaccination.

The term *variola* derives from the Latin *varius* (spotted) or *varus* (pimple): it was used for the first time in the sixth century by Bishop Marius of Avenches (Switzerland), when smallpox had already become endemic in Europe. In the Anglo-Saxon world, in the 10th century, the word poc or pocca, a bag or a pouch, described an exanthematous disease. With the appearance of syphilis in Europe at the end of the 15th century, writers began to use the prefix small to distinguish *variola*, *smallpox*, from *syphilis*, the great *pox* [12].

Mpox: a long-term global threat?

With the eradication of smallpox in 1980, and the subsequent cessation of smallpox vaccination, *Mpox* has emerged as the most important *Orthopoxvirus*, in terms of its possible public health impact; the case-fatality rate of the Congo basin strain is ≤ 10%, while that of the West African strain is < 1% [13].

The first MPXV genome sequences from the outbreak were reported from Portugal on May 19, 2022, and multiple additional sequences, which can shed light on virus circulation, are now available.

Initial phylogenetic analyses indicated that the 2022 outbreak was caused by the virus belonging to the clade MPXV II (former West African clade), which is less severe than clade I (former Congo Basin clade). These analyses have led to think that the current outbreak was caused by the recent introduction of the virus into communities in non-endemic MPXV countries. However, further studies that include additional MPXV genome sequences point to a different scenario [14].

Current data on the spread of cases outside countries where the virus is normally endemic suggests that *Mpox* could pose a long-term global threat.

On 23 July 2022, the Director-General of the WHO, Thedos Adhanom Ghebreyesus, issued an international public health alert regarding cases of monkeypox [15]. Indeed, within a few months, the number of individuals infected by monkeypox increased exponentially.

Mpox is a zoonosis, that is transmitted from animals to humans, with cases often found close to tropical rainforests where there are animals that carry the virus.

"The disease can also spread from humans to humans, through contact with bodily fluids, lesions on the skin or on internal mucosal surfaces, such as in the mouth or throat, respiratory droplets and contaminated objects" [16].

In humans, *Mpox* begins with non-specific symptoms, such as fever, headache, chills, asthenia, enlarged lymph nodes and muscle pain. Within three days, a rash appears, first involving the face and then spreading to other parts of the body, including the hands and feet. The skin lesions evolve in the form of papules, then vesicles, pustules and finally crusts. In most people, *Mpox* lasts for two to four weeks and heals completely.

Prior to the 2022 outbreak, the majority of cases of monkeypox had been reported in people living in central and western Africa. Almost all of the cases identified in subjects living outside Africa were linked to travel to countries where the disease was endemic or were due to contact with sick animals brought from Africa. Within a few months, the disease aroused interest in Europe and the United States.

The interest of the scientific community also focused on the modes of transmission of the disease, which seemed to affect mainly, though not exclusively, men who had sex with other men [17].

Although direct contact through sexual activity appears to have been the main mode of transmission during the 2022 outbreak, recent studies have shown that "Human-to-human transmission of monkeypox virus can occur through respiratory secretions, direct contact, vertical transmission, percutaneous transmission, or indirect contact through fomites" [18].

This declaration also seems to have curbed, to some

degree, the stigmatization of people affected by this disease.

Therefore, it is important "to disseminate precise communication to the entire population that must not be directed only to high-risk groups, *i.e.*, MSM, people living with HIV/AIDS (PLWHA), and the lesbian, gay, bisexual, transgender, and queer (or questioning), plus other sexual and gender identities (LGBTQI+ community)" [19].

At the same time, the WHO changed the name of the disease from Monkeypox to *Mpox*, as the term 'monkeypox' could be discriminatory, stigmatizing and misleading.

Indeed, when the outbreak of monkeypox expanded earlier this year, racist and stigmatizing language online, in other settings and in some communities was observed and reported to the WHO.

Thus, "Following a series of consultations with global experts, the WHO will begin using a new preferred term "*Mpox*" as a synonym for monkeypox. Both names will be used simultaneously for one year while "monkeypox" is phased out [20].

Discovered in 1958 in colonies of captive-bred research monkeys, the virus came to be known as "monkeypox", although the source of the disease was unknown. The first case of animal-to-human zoonotic MPV transmission was registered in 1970 in Zaire (now the Democratic Republic of Congo, DRC) in a 9-month-old baby boy [21-24]. Over the years, a few cases of monkeypox were recorded outside Africa, such as an outbreak in the United States of America in 2003 due to animals imported from Ghana [25] and sporadic travel-related cases registered in the UK, Singapore and Israel [26]. The WHO Bulletin reported over 6200 confirmed cases and 9400 suspected cases in 2020 and 2021, respectively [27, 28].

Moreover, these data are probably underestimated, owing to the lack of robust surveillance systems in endemic regions. However, little attention was paid to this disease until the WHO Director-General's international public health alert in July 2022.

In addition, as the African countries where the virus is endemic are developing countries, they have little or no possibility to monitor and report cases of monkeypox, the clinical symptoms of which resemble those of some other widespread diseases, such as syphilis and chickenpox. This lack of rigorous health surveillance may facilitate the spread of the epidemic.

In addition to *Mpox*, the Cowpox and Vaccinia viruses, which are used in vaccines against smallpox and are normally responsible for zoonoses, can also infect humans.

Alastrim, a disease that spread rapidly everywhere

Thanks to the extraordinary vaccination campaign implemented worldwide, not only human smallpox has been eradicated but also the clinically less serious form, *Alastrim* [29,30]. The name *Alastrim* is of Brasilian origin, being derived from a Portuguese word meaning to spread or strew about.

This term, introduced in the scientific language in 1910 by the Brazilian doctor Emilio Ribas, in the Portuguese language indicates "something that spreads rapidly everywhere" [31, 32].

Alastrim was also known as pseudovariola or whitepox, Kaffir pox [33] and by various other names.

Variola minor produced a milder illness with case-fatality rates of 1% or less, as opposed to 30% in the case of *Variola virus*. This is why it was used in antiquity in the variolation technique.

De Korte described it as "Cafri fever" for the first time in the late 19th century in South Africa. And in 1897 Chapin witnessed its presence in the United States of America. *Variola minor* became the prevalent variety in America, Europe and some areas of eastern and southern Africa [12].

In 1921, *Alastrim* struck Jamaica [34] and in November 1922 it appeared in French Guiana, where many cases were mistaken for chickenpox, given the many points of similarity between the two diseases. In a 1924 article by Stéphen Chauvet, a physician of internal medicine at the Paris Hospitals, *Alastrim* was described as an almost unknown disease, unmentioned in pathology textbooks. "Some seaports visited by steamships from Central America and the Antilles (Bordeaux, Saint Nazare, le Havre) have recently seen cases of an eruptive disease hitherto completely unknown in France, *Alastrim* […]" [35].

At the time of Dr. Chauvet, *Alastrim* also raised an important diagnostic problem: that of his relationship with smallpox, asserted by some and denied by others. From this theoretical problem important practical deductions necessarily arose regarding the curative and preventive treatment and the choice of prophylactic sanitary measures.

Clinically, after an incubation period of 10-14 days (like that of *Variola maior*), which however in some cases is reduced to 7 days, the infected person developed dermatitis.

The lesions were initially erythematous, subsequently papular, and then papulo-vesicular; in the following 1-2 days, centrally umbilicated pustular lesions appeared. The papules, which were fewer than in cases of *Variola maior*, first appeared on the face and then on the trunk, without itching. In addition to the skin lesions, the patient presented general malaise, digestive disturbances and a slight fever, which disappeared when the rash appeared (Fig. 1).

In his article, Stéphen Chauvet stated that *Alastrim* had a "*predilection for the black race*", unlike smallpox, smallpox and chickenpox, which "*affect all races without distinction*". However, the editorial staff of the journal inserted a note, specifying that: "*This article was in composition when Dr. Léon Bernard presented some preliminary clarifications on Alastrim to the Paris Academy of Medicine (October, 1923): this author now*

Fig. 1. Patient affected by Alastrim (from Chauvet S. L'Alastrim. 1924)
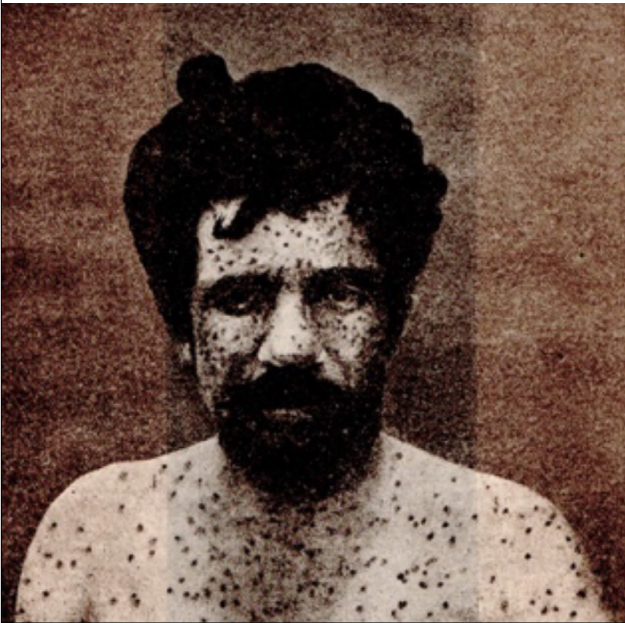
Fig. 2. Ali Maow Maalin, 1977, while infected with Alastrim (Wikipedia commons - public domain)
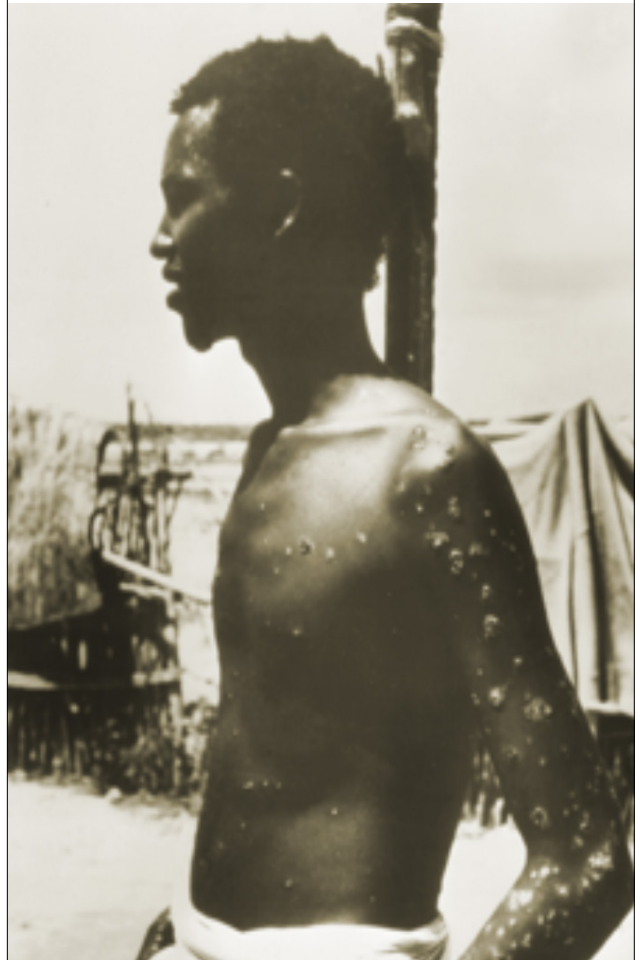
states that only negroes are affected. In reality, this statement, which Dr. Bernard absolutely insisted on, is completely wrong; the white race is affected just like blacks. Perhaps, as Dr. Blin observes, the black race is particularly sensitive; it is, however, more likely that blacks are affected more frequently owing to their lack of hygiene. We note that the photographs presented by Dr. Stéphen Chauvet in this article show a white sailor affected by Alastrim" [35].

Clearly, the content of this note and the terminology used are absolutely unacceptable. Nevertheless, the note shows that *Alastrim* long remained an almost unknown disease, so much so that doubts were raised as to whether the virus responsible actually belonged to the *Orthopoxvirus* family. Indeed, the linear double-stranded DNA sequences of the *Alastrim* virus genome were only determined in the 1960s [36].

Conclusion

It was precisely this virus that infected Ali Maow Maalin (1954-2013) (Fig. 2), the last person to be infected with *Variola minor*.

On 22 October 1977, Maalin, who was occasionally involved in smallpox vaccination campaigns organized by the WHO in Somalia, developed fever and headache, and was given antimalarial drugs. Four days later, a rash typical of smallpox appeared. However, presuming that Maalin had been vaccinated against smallpox, the doctors assumed he had chickenpox. After a few days, the symptoms began to indicate smallpox infection. However, not wishing to be placed in solitary confinement, Maalin did not report himself as a probable smallpox

patient; he therefore came into contact with numerous individuals. Eventually, the diagnosis of smallpox caused by *Variola minor* became clear, and was confirmed by laboratory tests. Containment measures were immediately implemented, first in the Merca region, where Maalin lived, and later throughout Somalia. On April 17, 1978, a communiqué from the WHO office in Mairobi stated: "Search complete. No cases discovered. Ali Maow Maalin is the world's last known smallpox case" [37].

Thus ended the story of smallpox, which, on 8 May 1980, was declared by the WHO to have been eradicated from the world! [38] And so it was *Alastrim* - a disease caused by the minor form of the *Variola virus* and far less well-known than human smallpox - that closed the story of an evil that had afflicted humanity since the dawn of time, striking terror into people's hearts.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

DO and MM conceived the study; DO designed the study; MM and DO drafted the manuscript. DO, MM and NLB performed a search of the literature.

All authors revised the manuscript; NLB and MB critically revised the manuscript. All authors have read and approved the latest version of the paper for publication. Furthermore: DO: conceptualization, and MM, DO, NLB: methodology, validation, and data curation; NLB, MB: formal analysis; MM and DO: original draft preparation; MM: review, DO editing.

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OCCUPATIONAL MEDICINE AND HYGENE

Prevalence and associated factors of depression, anxiety, and stress among academic medicine faculty in Kazakhstan: a Cross-sectional Study

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Keywords

Summary

Introduction. *Psychological distress refers to a set of painful mental and physical symptoms of anxiety and depression, which often coexist and coincide with common somatic complaints and chronic conditions. In Kazakhstan, mental disorders are the second leading cause of years lived with disability. Currently, medical education in Kazakhstan is undergoing comprehensive reform, which creates an additional burden on faculty, fostering mental health concerns.*
Methods. *A quantitative observational cross-sectional study was conducted in 6 large medical universities in Kazakhstan. Data were obtained from 715 faculty academics by using an online self-reported DASS-21. Statistical analysis was performed using the SPSS version 20.0. Bivariate and multivariate logistic regression analyses were applied to evaluate the relationship between predictor and outcome variables.*

Results. *The total prevalence of depression, anxiety, and stress was 40.6%, 41.3%, and 53.0%, respectively. Younger age (p = 0.002), female gender (p = 0.001), being single (p = 0.044) or in a relationship (p = 0.001), having chronic diseases (p < 0.001), holding Master (p = 0.036) or PhD degree (p = 0.040), employment status (p = 0.034), and being involved in additional activities (p = 0.049) were significantly associated with different dimensions of distress.*
Conclusions. *Nearly half of the study population reported symptoms of depression, anxiety, and stress. Due to the higher prevalence of psychological distress amongst academic medicine faculty, determined risk factors must be taken into consideration in developing policies for mental issues prevention.*

Introduction

Healthcare system in Kazakhstan has undergone substantial changes over the past years. Since gaining independence in 1991, the government has attempted to undertake multiple reforms in the healthcare model inherited from the Soviet Union. The health sector confronted plenty of challenges, struggling with insufficient funding, outdated equipment, limited flexibility of services, and poor quality of medical aid in the cornerstone [1,2]. To ensure the success of transformations made to date, medical education ought to align with specific health system demands [3].

The rapid growth of medical education facilities intensified intense competition between higher education institutions, which consistently predetermines the serious responsibility of academic staff for teaching and research work. Educators are pressurized with regular obligations that are constantly expanding to meet the requirements of the new time [4]. It is commonly believed that health professionals, acceding to teaching positions, already have the necessary skills, since their core mission comprises sharing knowledge in a specific area. In this respect, a huge proportion of employees enter the academic environment insufficiently prepared for the role of a teacher [5, 6].

Currently, medical education in Kazakhstan is undergoing comprehensive reform in shifting from a traditional seven-year program (five-year bachelors with further two-year internship) to a six-year model. The new model implies the continuing education program integrated with internship and masters studies and demands full-scale efforts to revise the learning outcomes. Therefore, developing and enhancing curricula apart from educational or clinical activities creates an additional burden on faculty, which may foster mental health concerns. From this perspective, the investigation of factors associated with the psychological distress of faculty is becoming an evolving area of research around the world.

Psychological distress (PD) refers to a set of painful mental and physical symptoms of anxiety and depression, which often coexist and coincide with common somatic complaints and chronic conditions [7, 8]. The Global Burden of Disease 2019 study has denoted that depressive and anxiety disorders were the

leading causes of burden worldwide and ranked among the top 25 disability causes, remaining high across the entire lifespan. What is more devastating, an in-depth analysis demonstrated that the estimated cases of mental disorders had grown by 48.1% between 1990 and 2019 [9], and have the tendency to rise due to global disruption brought up by the COVID-19 pandemic [10]. According to the COVID-19 Mental Disorders Collaborators report, the pandemic triggered an increase in depressive and anxiety disorders by about 25% [11].

In Kazakhstan, mental disorders (in particular, depressive disorders) are the second leading cause of years lived with disability (YLD) [12], but as in many countries of Central Asia are not given due consideration. Cultural patterns and traditional beliefs, along with the Soviet system legacy developed certain attitudes towards mental health, including social stigmatization and neglect [13, 14]. The systematic review overviewing stigma towards psychiatric illnesses in six Asian societies has established that people with such health conditions were considered dangerous and aggressive and therefore discriminated against [15]. In most eastern cultures, mental disorders are perceived as a personal weakness and occasionally even as a family flaw. Fear of public labeling, prejudice, social abandonment, and withdrawal from civil life is found to be a strong barrier to seeking professional help [16, 17]. Globally, more than 70% of people with mental disorders do not receive appropriate treatment [18]. Nevertheless, 3.72% of the Kazakhstani population suffers from clinical depression and 2.26% from anxiety, which brings the country to rank second among countries in Central Asia on disability-adjusted life years (DALYs) after Uzbekistan and to rank 20th in global suicide rates [12, 19].

We have not identified studies pertaining to the prevalence and predictors of psychological distress amongst health sciences faculty in Kazakhstan or other countries of the post-Soviet region. Therefore, little to nothing is known about measures for addressing mental health issues in the era of curricular reforms. To the best of our knowledge, there was not any equivalent study conducted in Kazakhstan to investigate the borderline mental disorders among academic medicine faculty teachers. Hence, the aim of our study was to explore the current prevalence and associated factors of psychological distress amongst medical universities academic staff in Kazakhstan. Given the significance of mental health problem among representatives of medical education sector and limited number of studies dedicated to this issue, our study attempted to shed light on the current mental status of educators and factors that contribute to it. Moreover, early diagnostics of borderline mental disorders and timely response could be attained by using the appropriate instruments, including the DASS-21. Nevertheless, mental well-being among academic medicine faculty ought to be scrutinized more precisely. In light of the fact that this matter has not been given due attention, our study may contribute to further investigations.

Methods

STUDY DESIGN

This quantitative observational cross-sectional study was conducted over 3 months from October to December 2021 in Kazakhstan. Selecting this period was justified by the duration of the fall semester in Kazakh medical universities (from September to January). Therefore, the workload in the first and last months of the semester is particularly escalated, which could become an additional matter for psychological distress and distort real results. The manuscript was prepared following the STROBE guidelines for cross-sectional studies.

STUDY SAMPLE

The total study population was represented by 715 educators from six large medical universities from different regions (Fig. 1). The sample size was calculated by EpiInfo version 7.0 software, with an expected frequency of 30% and a confidence interval (CI) of 95%. The calculated sample size was 596, which was inflated by 20% with regard to data loss. We used a convenience sampling strategy in our study. Eligibility criteria comprised 1) willingness to participate in a survey, 2) present position of a medical university teacher, and 3) absence of clinical manifestations of mental disorders. Educators who 1) refused to participate, 2) had an annual principal vacation, and 3) were on a decree or sick leave were excluded from the study.

STUDY INSTRUMENT

The Depression Anxiety Stress Scale (DASS-21) was used to estimate psychological distress. DASS-21 is a valid three-dimensional self-reporting instrument for the evaluation of depression, anxiety, and stress level. The psychometric properties of the questionnaire have been proven in numerous studies. The reliability and internal consistency of DASS-21 demonstrated its practicability in both clinical and non-clinical settings [20-25].

DASS was developed by Lovibond S.H. and Lovibond P.F. in 1995 and previously consisted of 42 items [26]. Eventually, it was shortened to a 21-item form with 7 items on each subscale. In contrast to other questionnaires aimed at the evaluation of borderline mental disorders, DASS-21 is designed to assess the combined effect of depression, anxiety, and stress, since these disorders predominantly have a similar origin and are strongly correlated with each other.

The depression subscale assesses feelings of melancholy, hopelessness, lack of motivation and interest in life, anhedonia, and inertia. The anxiety subscale includes measuring situational anxiety, fear, and excitement. The stress subscale evaluates agitation, irritability, overreaction, and nervousness.

DATA COLLECTION

An online self-reported questionnaire was administered to collect data. The link with a survey was distributed among university teachers via WhatsApp messenger.

Fig. 1. Geographical spread of large medical universities in Kazakhstan

Aktobe Region
- West Kazakhstan Marat Ospanov Medical University

Akmola Region
- Astana Medical University

Karaganda Region
- Karaganda Medical University

East Kazakhstan Region
- Semey Medical University

Almaty region
- Asfendiyarov Kazakh National Medical University
- The Kazakhstan School of Public Health
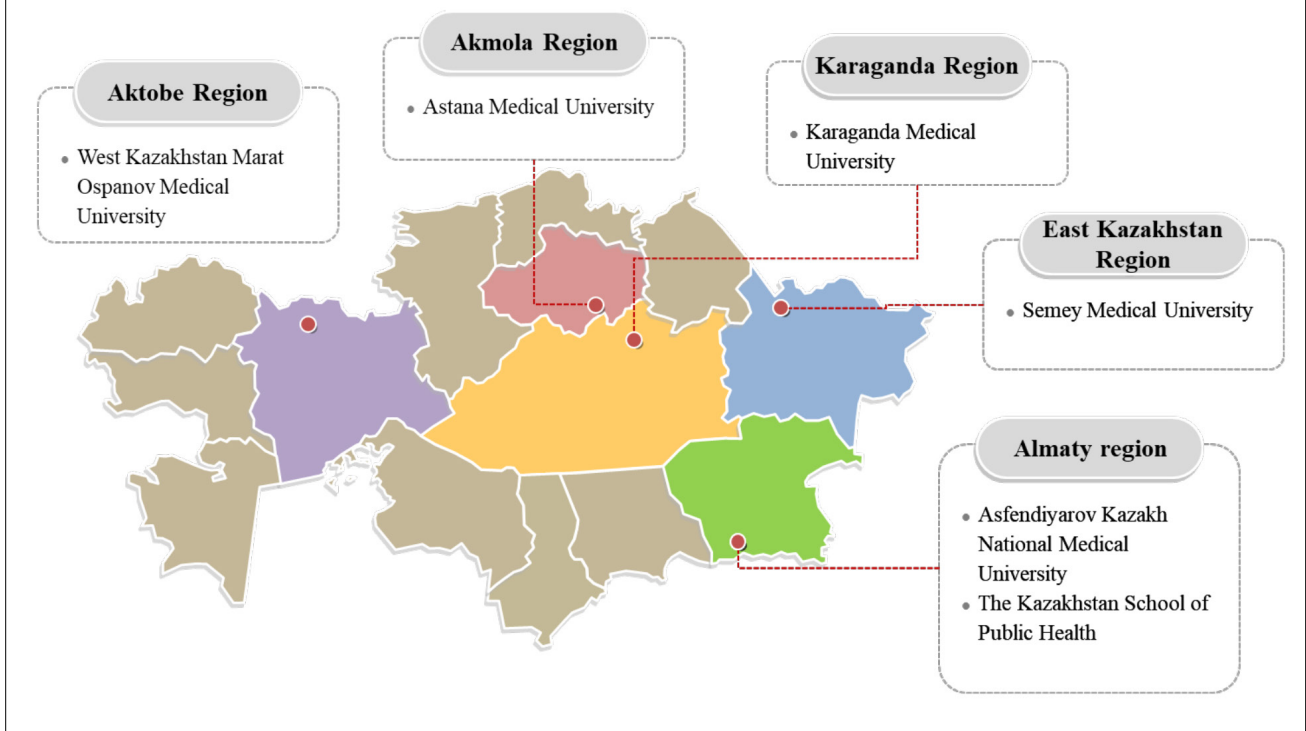
The first section of the form involved socio-demographic characteristics (such as age, sex, marital status, having children, having a spouse or partner with the same occupation, health status, current position, work experience, department focus, employment status, academic degree or rank, and additional activity).

The second section included statements of the DASS-21 form. The study participants were asked to read each statement and rate the applicability to their emotional state in the past week. Responses were rated on a 4-point Likert scale from 0 (does not apply to me at all) to 3 (most of the time applies to me). The scoring 0-4 for depression scale was evaluated as a normal condition, 5-6 mild, 7-10 moderate, 11-13 severe, and > 14 extremely severe depression. The anxiety scale was scored as follows: 0-3 normal condition, 4-5 mild, 6-7 moderate, 8-9 severe, and > 10 extremely severe anxiety. The stress scale scoring was the following: 0-7 normal condition, 8-9 mild, 10-12 moderate, 13-16 severe, and > 17 extremely severe stress. Therefore, the scores of 5, 4, and 8 were applied as cut-off points for depression, anxiety, and stress dimensions, respectively.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 20.0. In the course of the study, quantitative and qualitative data were obtained. The normality of distribution was analyzed using the Kolmogorov-Smirnov test. Data analysis included descriptive and inferential statistics. Pearson's correlation test was performed to analyze the correlation between three subscales of the DASS-21.

At the initial stage, we applied descriptive statistics and bivariate analysis to examine the association between outcome variables and socio-demographic data. A Chi-square test was conducted for bivariate analysis of categorical variables. The means and standard deviations (SD) were calculated for continuous variables, as well as categorical variables were presented in frequencies and percentages, along with p-values, odds ratios (OR), and 95% confidence intervals (CI).

Next, multinomial logistic regression via the forced entry procedure was run to evaluate the relationship between predictor and outcome variables. Variables with a p-value of less than 0.25 at the initial stage were included in the final regression model, as recommended by Bursac et al. [27]. The test for multicollinearity among all variables was conducted prior to data analysis. The cutoff value for variance inflation factor (VIF) of < 5 was accepted, as recommended by Vatcheva et al. [28]. A p-value of 0.05 was considered statistically significant for the final model.

Ethics statement

The study was conducted in compliance with the Declaration of Helsinki. Ethical approval was obtained from the Local Ethics Committee of Semey Medical University (No. 2-28-10-2020). Official letters with requests for permission to survey the faculty were sent to each medical university. Participation was voluntary and anonymous to ensure the honesty and integrity of the research. The informed consent outlined the essence of the study, the purpose, objectives, the role of the participants, and their right to withdraw from the study at any moment. Moreover, study participants

were informed that the data collected would be kept confidential and stored in a computer file in coded form. Likewise, any information published would be presented in integers and percentages.

Results

Psychometric properties of the DASS-21

Reliability analysis illustrated a high internal consistency of scales used. Integral Cronbach's alpha for the DASS-21 was 0.949 (0.899 for depression subscale, 0.820 for anxiety subscale, and 0.907 stress subscale). A strong correlation has been revealed between all subscales: depression and anxiety (p = 0.762; p < 0.001), depression and stress (p = 0.806; p < 0.001), and anxiety and stress (p = 0.752; p < 0.001).

Descriptive statistics

Overall, 715 faculty members completed the online survey. Participants mean age ± SD was 41.12 ± 11.18, ranging from 23 to 78 years. The majority of responders were females (67.3%). The most common marital status was being married (61.4%). Furthermore, 28.3% of educators reported having a spouse or partner occupying the same position (medicine or teaching). Nearly three-quarters (73.8%) reported having children. Slightly over half of all responders (54.3%) instructed in theoretical and basic disciplines. Full-time staff represented the vast majority (77.9%) of the study sample. The most popular additional activity was research work, which was selected by nearly a quarter of teachers (22.4%).

The mean score ± SD in the depression subscale was 4.36 ± 4.21, in the anxiety subscale was 3.49 ± 3.08, and in the stress subscale was 7.87 ± 4.57. Descriptive analysis revealed various levels of psychological distress amongst the study population. Altogether, the prevalence of depression, anxiety, and stress was 40.6%, 41.3%, and 53.0%, respectively.

Inferential statistics

We investigated the association between the socio-demographic characteristics of responders and the DASS-21 subscales (Tab. I). Ten variables were found to be significantly associated with depression and anxiety: age (p < 0.001), sex (p < 0.001), marital status (p < 0.001), having children (p < 0.001), having chronic diseases (p = 0.029 for DASS-D; p < 0.001 for DASS-A), position (p < 0.001 for DASS-D; p = 0.004 for DASS-A), work experience (p < 0.001), employment status (p < 0.001), academic rank (p < 0.001), and being involved in additional activities (p = 0.013 for DASS-D; p = 0.040 for DASS-A). Eight variables were significantly associated with stress: age (p < 0.001), marital status (p < 0.001), having children (p < 0.001), position (p = 0.020), work experience (p < 0.001), employment status (p < 0.001), academic rank (p < .001), and being involved in additional activities (p < 0.001).

Regression models for factors associated with psychological distress

Factors that were significant in the previous binary analysis were included in the final models as independent variables. Table II details the regression models for the DASS-21 subscales. In depression multivariate logistic regression model, age under 40 (AOR = 2.74; 95% CI 1.44-5.23), being single (AOR = 3.91; 95% CI 1.04-14.74) or in a relationship (AOR = 12.22; 95% CI 2.93-51.01), holding Master (AOR = 2.08; 95% CI 1.05-4.12) or PhD degree (AOR = 2.22; 95% CI 1.04-4.76), and being involved in various additional activities (AOR = 10.89; 95% CI 1.01-117.52) was associated with the risk of depression. Also, the male gender (AOR = 0.48; 95% CI 0.32-0.74) and the absence of chronic diseases (AOR = 0.37; 95% CI 0.25-0.55) were associated with a lower risk of depression.

In anxiety model, the male gender (AOR = 0.51; 95% CI 0.34-0.76), the absence of chronic diseases (AOR = 0.27; 95% CI 0.19-0.40), and working full-time (AOR = 0.61; 95% CI 0.38-0.96) were associated with lower odds to report anxiety. However, as in the depression model, holding Master (AOR = 2.33; 95% CI 1.25-4.34) and PhD degrees (AOR = 3.71; 95% CI 1.83-7.52) was associated with the higher risk of anxiety (Tab. III).

Results of the regression model for stress are demonstrated in Table IV. It was established that being in a relationship (AOR = 13.96; 95% CI 2.90-67.08), married (AOR = 4.45; 95% CI 1.23-16.05), or divorced (AOR = 9.99; 95% CI 2.50-39.82) were significantly associated with stress, along with holding PhD degree (AOR = 2.77; 95% CI 1.39-5.52) and combining the teaching with other activities (AOR = 5.52; 95% CI 1.01-30.13).

Discussion

Our study was principally aimed at the evaluation of the prevalence and associated factors of psychological distress in Kazakhstan medical faculty academics sample. Since both the education and healthcare sectors are vulnerable to distress, academic medicine faculty are at higher risk of mental health issues [29]. Our results illustrated the total prevalence of depression, anxiety, and stress of 40.6%, 41.3%, and 53.0%, respectively. These findings are corresponding to prior studies that explored the prevalence of psychological distress amongst educators [30-32]. Silva et al. [33] in their systematic review stated that the prevalence of anxiety ranged from 10% to 49.4%, depression from 15.9% to 28.9%, and stress from 12.6% to 50.6% around the world. The higher levels of distress in Kazakhstan may be due to the lack of attention given to mental health and psychological support.

Another possible reason for the higher rates of psychological distress may be the global disruption due to COVID-19 pandemic. Since epidemiological situation in Kazakhstan remained unstable for the period of data collection, we suppose that drastic

Tab. I. The association between socio-demographic characteristics of responders and the DASS-21 subscales.

Variable	n (%)	Depression		Anxiety		Stress	
		M ± SD	p-value[a]	M ± SD	p-value[a]	M ± SD	p-value[a]
Age			< 0.001*		< 0.001*		< 0.001*
< 40	379 (53)	6.2 ± 4.4		4.1 ± 3.3		9.4 ± 4.6	
> 40	336 (47)	2.9 ± 3.2		2.8 ± 2.6		6.2 ± 3.9	
Sex			< 0.001*		< 0.001*		0.527
Male	234 (32.7)	3.4 ± 3.4		2.8 ± 2.6		7.7 ± 3.7	
Female	481 (67.3)	5.3 ± 4.4		3.8 ± 3.2		8.0 ± 4.9	
Marital status			< 0.001*		<0.001*		< 0.001*
Single	111 (15.5)	5.9 ± 4.9		3.9 ± 3.5		8.3 ± 5.4	
In a relationship	74 (10.3)	8.9 ±4.5		5.3 ± 3.3		11.7 ± 3.9	
Married	439 (61.4)	3.8 ± 3.6		3.1 ± 2.8		7.3 ± 4.2	
Divorced	66 (9.2)	4.4 ± 3.8		3.7 ± 3.3		8.0 ±4.3	
Widowed	25 (3.5)	2.4 ± 2.1		2.4 ± 1.6		4.8 ± 2.9	
Spouse or partner occupying the same position			0.650		0.253		0.258
No	493 (71.7)	4.5 ± 4.2		3.5 ± 3.1		7.6 ± 4.6	
Yes	195 (27.3)	4.7 ± 4.2		3.4 ± 3.0		8.4 ± 4.2	
Children			< 0.001*		< 0.001*		< 0.001*
No	187 (26.2)	6.9 ± 4.9		4.5 ± 3.3		9.8 ± 5.0	
1	195 (27.3)	4.8 ± 3.9		3.4 ± 3.1		8.1 ± 4.4	
2	209 (29.2)	3.5 ± 3.3		3.0 ± 2.8		7.0 ± 3.9	
3 or more	124 (17.3)	2.9 ± 3.5		2.8 ± 2.8		6.1 ± 3.9	
Chronic diseases			0.029*		<0.001*		0.359
No	417 (58.3)	4.2±3.9		2.9 ± 2.8		7.5 ± 4.4	
Yes	298 (41.7)	5.2 ± 4.6		4.3 ± 3.3		8.3 ± 4.7	
Position			<0.001*		0.004*		0.020*
Assistant teacher	474 (66.3)	5.2 ± 4.6		3.9 ± 3.4		8.1 ± 5.0	
Head teacher	154 (21.6)	4.3 ± 3.4		2.9 ± 2.3		7.9 ± 3.7	
Head of the department	87 (12.2)	2.4 ± 2.3		2.6 ± 1.8		6.7 ± 3.0	
Work experience			< 0.001*		< 0.001*		< 0.001*
Less than 1 year	24 (3.4)	7.3 ± 5.4		5.3 ± 4.1		9.3 ± 6.4	
1-5 years	162 (22.7)	7.0 ± 4.8		4.4 ± 3.4		10.0 ± 4.9	
5-10 years	171 (23.9)	5.6 ± 4.1		3.8 ± 3.2		9.0 ± 4.4	
More than 10 years	358 (50.1)	2.9 ± 3.0		2.8 ± 2.6		6.3 ± 3.7	
Department focus			0.479		0.770		0.802
Theoretical/basic	388 (54.3)	4.9 ± 4.4		3.5 ± 3.1		7.8 ± 4.8	
Clinical	327 (45.7)	4.3 ± 4.0		3.5 ± 3.0		7.9 ± 4.3	
Employment status			< 0.001*		< 0.001*		< 0.001*
Full-time	557 (77.9)	4.2 ± 3.9		3.2 ± 3.0		7.3 ± 4.4	
Part-time	158 (22.1)	6.2 ± 4.8		4.4 ± 3.2		9.9 ± 4.6	
Academic rank			< 0.001*		< 0.001*		< 0.001*
No	174 (24.3)	4.3 ± 4.0		3.4 ± 3.1		7.5 ± 4.7	
Master	260 (36.4)	6.2 ± 4.5		4.1 ± 3.2		8.9 ± 5.0	
PhD	93 (13.0)	4.9 ± 3.5		3.9 ± 3.1		9.2 ± 3.4	
Professor/Candidate	188 (26.3)	2. 6± 3.2		2.6 ± 2.5		6.1 ± 3.7	
Additional activities			0.013*		0.040*		< 0.001*
No	113 (15.8)	3.4 ± 4.3		2.8 ± 3.5		5.0 ± 4.8	
Clinical activities	205 (28.7)	4.5 ± 4.0		3.5 ± 3.1		7.9 ± 4.1	
Research work	160 (22.4)	5.1 ± 4.7		3.8 ± 3.1		8.7 ± 4.8	
Methodological work	142 (19.9)	5.2 ± 3.8		3.4 ± 2.8		8.7 ± 3.9	
Educative activities	44 (6.2)	5.4 ± 5.0		3.8 ± 3.2		7.7 ± 5.2	
Mixed activities	43 (6.0)	4.3 ± 2.8		3.8 ± 2.1		9.8 ± 2.8	
Other	8 (1.1)	3.0 ± 2.2		3.9 ± 2.4		8.1 ± 5.1	

n: number of responders, M: mean, SD: standard deviation; [a] Using Pearson Chi-square test; * p-value is significant.

Tab. II. Multinomial logistic regression of the depression subscale with demographic data and work factors.

Variable	COR (95% CI)	p-value	AOR (95% CI)	p-value
Age				
< 40	5.74 (4.10-8.04)	< 0.001*	2.74 (1.44-5.23)	0.002*
> 40	1 (reference)		1 (reference)	
Sex				
Male	0.55 (0.40-0.77)	<0.001*	0.48 (0.32-0.74)	0.001*
Female	1 (reference)		1 (reference)	
Marital status				
Single	6.18 (1.99-19.17)	0.002*	3.91 (1.04-14.74)	0.044*
In a relationship	24.64 (7.23-83.90)	< 0.001*	12.22 (2.93-51.01)	0.001*
Married	2.48 (0.84-7.37)	0.101	1.90 (0.60-6.02)	0.279
Divorced	3.00 (0.92-9.77)	0.068	1.96 (0.56-6.88)	0.296
Widowed	1 (reference)		1 (reference)	
Children				
No	5.73 (3.4209.59)	< 0.001*	0.74 (0.30-1.81)	0.504
1	2.88 (1.74-4.78)	< 0.001*	1.17 (0.64-2.15)	0.610
2	1.26 (0.75-2.11)	0.393	0.76 (0.42-1.39)	0.376
3 or more	1 (reference)		1 (reference)	
Chronic diseases				
No	0.71 (0.53-0.97)	0.029*	0.37 (0.25-0.55)	<0.001*
Yes	1 (reference)		1 (reference)	
Position				
Assistant teacher	5.37 (2.84-10.14)	< 0.001*	1.79 (0.80-4.02)	0.159
Head teacher	3.88 (1.95-7.75)	< 0.001*	1.21 (0.51-2.86)	0.663
Head of the department	1 (reference)		1 (reference)	
Work experience				
Less than 1 year	8.86 (3.55-22.14)	< 0.001*	2.24 (0.68-7.33)	0.184
1-5 years	6.37 (4.24-9.58)	< 0.001*	1.66 (0.82-3.39)	0.162
5-10 years	4.35 (2.94-6.44)	< 0.001*	1.58 (0.85-2.94)	0.151
More than 10 years	1 (reference)		1 (reference)	
Employment status				
Full-time	0.49 (0.34-0.69)	< 0.001*	0.93 (0.57-1.52)	0.781
Part-time	1 (reference)		1 (reference)	
Academic rank				
No	3.38 (2.06-5.54)	< 0.001*	1.15 (0.57-2.34)	0.699
Master	7.07 (4.46-11.21)	< 0.001*	2.08 (1.05-4.12)	0.036*
Ph.D.	4.53 (2.58-7.96)	< 0.001*	2.22 (1.04-4.76)	0.040*
Professor/ Candidate	1 (reference)		1 (reference)	
Additional activities				
No	2.53 (0.30-21.43)	0.394	3.08 (0.30-31.65)	0.343
Clinical activities	4.86 (0.59-40.23)	0.143	6.43 (0.64-64.77)	0.114
Research work	5.04 (0.61-41.96)	0.134	4.75 (0.47-48.05)	0.187
Methodological work	6.08 (0.73-50.70)	0.095	6.23 (0.62-62.67)	0.121
Educative activities	6.39 (0.73-56.38)	0.095	5.30 (0.49-57.63)	0.171
Mixed activities	6.68 (0.76-59.05)	0.088	10.89 (1.01-117.52)	0.049*
Other	1 (reference)		1 (reference)	

COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence intervals; * p-value is significant.

changes in people's daily life may have challenged their mental health. Medical faculty members were particularly hit by the pandemic: most of the physicians overworked in the frontline, struggled with shifting to the distant learning, creating digital content for new training format, along with poor technical facilities and deficient internet connection. A systematic review and meta-analysis by Zeng et al. [34] investigating long term sequalae of COVID-19 pandemic highlighted escalation of depression, anxiety, post-traumatic stress disorder, and cognitive impairments within up to 12 months after infection. The COVID-19 Mental Disorders Collaborators report [10] showed more than 30% increase in the prevalence depressive and anxiety disorders in Kazakhstan during the outbreak.

A wide range of factors associated with depression, anxiety, and stress has been revealed in literature,

Tab. III. Multinomial logistic regression of the anxiety subscale with demographic data and work factors.

Variable	COR (95% CI)	p-value	AOR (95% CI)	p-value
Age				
< 40	2.16 (1.59-2.93)	< 0.001*	1.40 (0.74-2.65)	0.298
> 40	1 (reference)		1 (reference)	
Sex				
Male	0.51 (0.37-0.72)	< 0.001*	0.51 (0.34-0.76)	0.001*
Female	1 (reference)		1 (reference)	
Marital status				
Single	2.53 (0.98-6.52)	0.056	1.66 (0.52-5.29)	0.395
In a relationship	5.04 (1.86-13.66)	0.001*	2.95 (0.88-9.89)	0.080
Married	1.39 (0.57-3.40)	0.471	1.51 (0.57-4.00)	0.407
Divorced	2.14 (0.79-5.82)	0.135	1.66 (0.56-4.86)	0.360
Widowed	1 (reference)		1 (reference)	
Children				
No	3.69 (2.25-6.04)	< 0.001*	1.94 (0.83-4.53)	0.125
1	1.84 (1.13-3.00)	0.015*	1.26 (0.71-2.26)	0.439
2	1.61 (0.99-2.62)	0.056	1.53 (0.89-2.63)	0.126
3 or more	1 (reference)		1 (reference)	
Chronic diseases				
No	0.41 (0.30-0.56)	< 0.001*	0.27 (0.19-0.40)	< 0.001*
Yes	1 (reference)		1 (reference)	
Position				
Assistant teacher	2.06 (1.25-3.39)	0.005*	1.15 (0.58-2.27)	0.692
Head teacher	1.38 (0.78-2.43)	0.270	0.71 (0.34-1.49)	0.365
Head of the department	1 (reference)		1 (reference)	
Work experience				
Less than 1 year	4.28 (1.78-10.29)	0.001*	1.93 (0.61-6.05)	0.262
1-5 years	2.55 (1.74-3.73)	< 0.001*	1.02 (0.50-2.09)	0.954
5-10 years	1.75 (1.21-2.55)	0.003*	0.92 (0.49-1.71)	0.780
More than 10 years	1 (reference)		1 (reference)	
Employment status				
Full-time	0.47 (0.33-0.67)	< 0.001*	0.61 (0.38-0.96)	0.034*
Part-time	1 (reference)		1 (reference)	
Academic rank				
No	1.65 (1.05-2.57)	0.029*	1.52 (0.80-2.87)	0.202
Master	2.94 (1.96-4.40)	< 0.001*	2.33 (1.25-4.34)	0.008*
Ph.D.	2.70 (1.61-4.54)	< 0.001*	3.71 (1.83-7.52)	< 0.001*
Professor/candidate	1 (reference)		1 (reference)	
Additional activities				
No	0.26 (0.06-1.14)	0.074	0.30 (0.06-1.54)	0.148
Clinical activities	0.42 (0.10-1.79)	0.239	0.52 (0.10-2.61)	0.426
Research work	0.47 (0.11-2.02)	0.308	0.375 (0.08-1.88)	0.233
Methodological work	0.40 (0.09-1.75)	0.225	0.43 (0.09-2.15)	0.302
Educative activities	0.50 (0.11-2.36)	0.381	0.43 (0.08-2.40)	0.333
Mixed activities	0.83 (0.18-3.94)	0.818	1.04 (0.19-5.67)	0.961
Other	1 (reference)		1 (reference)	

COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence intervals; * p-value is significant

comprising both socio-demographic and work-related aspects. Our study identified that the women were at nearly 2 times higher risk of developing depression (AOR = 0.48; 95% CI 0.32-0.74) and anxiety (AOR = 0.51; 95% CI 0.34-0.76). Likewise, previous investigations enlightened that females have a tendency to report higher distress levels. This may be reasoned by the "double shift" phenomenon, when occupational risk factors overlap with home stressors, such as housework, childcare and upbringing, care for elderly family members, and many others [35-37].

Another socio-demographic determinant of poor mental health was younger age. Even though prior studies reported diverse findings regarding age and distress association [38], the majority of results indicated that younger faculty members have higher odds of reporting distress symptoms [39-42]. In our study, the faculty under the age of 40 were significantly associated with

Tab. IV. Multinomial logistic regression of the stress subscale with demographic data and work factors

Variable	COR (95% CI)	p-value	AOR (95% CI)	p-value
Age				
< 40	3.79 (2.78-5.17)	< 0.001*	1.76 (0.95-3.24)	0.071
> 40	1 (reference)		1 (reference)	
Marital status				
Single	10.36 (2.93-36.68)	< 0.001*	3.18 (0.73-13.79)	0.123
In a relationship	65.50 (14.74-248.28)	< 0.001*	13.96 (2.90-67.08)	0.001*
Married	6.37 (1.88-21.58)	0.003*	4.45 (1.23-16.05)	0.023*
Divorced	12.03 (3.26-44.34)	< 0.001*	9.99 (2.50-39.82)	0.001*
Widowed	1 (reference)		1 (reference)	
Children				
No	4.98 (3.05-8.13)	< 0.001*	2.18 (0.90-5.29)	0.085
1	2.12 (1.34-3.37)	0.001*	1.03 (0.59-1.80)	0.921
2	1.46 (0.92-2.30)	0.107	1.10 (0.66-1.84)	0.701
3 or more	1 (reference)		1 (reference)	
Position				
Assistant teacher	1.88 (1.18-3.00)	0.008*	0.93 (0.49-1.77)	0.816
Head teacher	1.97 (1.15-3.37)	0.013*	0.95 (0.47-1.91)	0.877
Head of the department	1 (reference)		1 (reference)	
Work experience				
Less than 1 year	3.96 (1.60-9.81)	0.003*	1.80 (0.55-5.90)	0.329
1-5 years	4.24 (2.83-6.36)	< 0.001*	1.29 (0.63-2.63)	0.484
5-10 years	2.87 (1.97-4.19)	< 0.001*	1.07 (0.58-2.00)	0.824
More than 10 years	1 (reference)		1 (reference)	
Employment status				
Full-time	0.34 (0.23-0.50)	< 0.001*	0.56 (0.34-0.90)	0.018*
Part-time	1 (reference)		1 (reference)	
Academic rank				
No	2.24 (1.46-3.43)	< 0.001*	1.23 (0.66-2.29)	0.522
Master	3.86 (2.59-5.75)	< 0.001*	1.70 (0.93-3.11)	0.087
PhD	5.35 (3.10-9.20)	< 0.001*	2.77 (1.39-5.52)	0.004*
Professor/Candidate	1 (reference)		1 (reference)	
Additional activities				
No	0.30 (0.07-1.28)	0.103	0.35 (0.07-1.65)	0.182
Clinical activities	1.14 (0.28-4.66)	0.860	1.13 (0.25-5.19)	0.874
Research work	1.50 (0.36-6.22)	0.576	1.25 (0.27-5.76)	0.771
Methodological work	1.54 (0.37-6.39)	0.555	1.46 (0.32-6.73)	0.625
Educative activities	1.10 (0.24-4.94)	0.906	0.94 (0.18-4.79)	0.937
Mixed activities	4.38 (0.90-21.34)	0.068	5.52 (1.01-30.13)	0.049*
Other	1 (reference)		1 (reference)	

COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence intervals; * p-value is significant.

depression symptoms (AOR = 2.74; 95% CI 1.44-5.23). This may be explained by the possible greater resilience and emotional stability of older people to the impact of stress. Besides, older faculty more often tend to be associate or full professors. Ahmady et al. [43] assume that professors are more experienced and do not have role stagnation compared to other ranks.

Our findings in multinomial logistic regression showed that depression was higher in educators who were single (AOR = 3.91; 95% CI 1.04-14.74) or in a relationship (AOR = 12.22; 95% CI 2.93-51.01). Despite the limited research exploring the association between mental health and marital status, some authors imply that being married may be buffering negative effects of occupational hazards [44-46]. Interestingly, these findings were established in eastern cultures (Turkey, Iran, United Arab Emirates), where the institution of marriage and family is of great importance. Therefore, we suppose that having a partner and being involved in household routine, but not registering formal marriage may serve as a risk factor for depressive symptoms in the cultural context of Kazakhstan.

According to our findings, educators suffering from chronic illnesses accumulated higher scores of depression and anxiety (p < 0.001). This was fairly anticipated, since suffering from chronic diseases for a long time may lead to distress symptoms. Our results are concordant with the latest studies of Santamaría et al. [47] and Silva et al. [33], devoted to scrutinizing the predictors of distress in teachers.

Moreover, our research has attempted to ascertain work-related determinants of psychological distress. In our sample of faculty academics, employment status was associated with stress (p = 0.018). Part-time educators were at nearly 2 times higher risk of stress in comparison with their full-time counterparts. This is consistent with the findings of Reevy and Deason [48], claiming that lower wages, failure to apply for a full-time faculty position, and low organizational commitment were potential risk factors for adverse outcomes.

We obtained interesting results regarding the association of psychological distress with academic rank. Our study identified that faculty with a Master and PhD degree were at higher risk of being depressed and anxious. Along with this, PhD educators were 2.77 times more prone to be stressed (p < 0.004). This may be possibly explained by the higher responsibility of PhD holders in advancing research at the departments, particularly in clinical departments, and attracting students and postgraduates for scientific work. According to Bell et al. [49], PhD faculty received half of all scholarly funding (50.2%), compared to 15.2% of MD faculty. Hurley et al. [50] noted that PhD faculty had 1.3 times more publications than MD (p = 0.0061), which made them the frontline supporters of the academic mission of the departments. University administration demands may put tremendous pressure on academics, who are forced to publish and generate clinical revenue along with teaching.

Our findings showed that combining various activities such as clinical, scientific, methodological, or educative obligations was significantly and positively associated with depression (AOR = 10.89; 95% CI 1.01-117.52) and stress (AOR = 5.52; 95% CI 1.01-30.13). This was somewhat expected due to the higher workload on faculty who mix teaching with extracurricular work. Besides, this category of faculty is more prone to hold academic degrees, which makes them responsible for departmental research projects, clinical volunteer work, curricula development, and tutoring.

To the best of our knowledge, this is the first study aimed at evaluating the prevalence of depression, anxiety, and stress amongst medical faculty staff in Kazakhstan. Additionally, none of the existing studies explored the occupational predictors of distress in equivalent samples. Our findings have provided constructive information about the prevalence of depression, anxiety, and stress, and their association with socio-demographic and job-related factors. Furthermore, the results shed light on the current mental health concerns of medical educators in Kazakhstan.

The study has several limitations. Firstly, data were obtained using a self-reported online questionnaire. Although the DASS-21 is a valid research instrument, the reliability of results might have been affected due to responders' inaccuracy in completing the survey. Besides, we have not confirmed our results with psychiatrists, and therefore the actual prevalence and severity of depression, anxiety, and stress may be lower or higher than in self-reported surveys. Secondly, income was not included in the study, although could

affect distress level. Thirdly, the study design was cross-sectional, hence there was no possibility to identify cause and effect relationships between variables. There is a need for longitudinal studies to address causal issues more congruously.

Conclusions

Mental health problems have become an increasingly important research topic in recent years. In our investigation, nearly half of the study population reported symptoms of depression, anxiety, and stress. Similar to previous studies, women suffered more from depression and anxiety rather than men. Holding academic degrees was significantly associated with all dimensions of distress. Due to the higher prevalence of psychological distress amongst academic medicine faculty, determined risk factors must be taken into consideration in developing policies for mental issues prevention. Moreover, it is recommended to conduct further investigations to reveal other paramount predictors of distress in larger samples.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

AU, AM: conceptualization. SM: data curation. AU, AB: formal analysis. AM, AB: methodology. AU, LM: visualization. AM, AB: supervision. AU: writing – original draft; AU, AM, SM, LM, LP, AB: writing – review & editing. SM: project administration.

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NON-COMUNICABLE DISEASES

Longitudinal machine learning model for predicting systolic blood pressure in patients with heart failure

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Keywords

Summary

Objective. *Systolic blood pressure (SBP) strongly indicates the prognosis of heart failure (HF) patients, as it is closely linked to the risk of death and readmission. Hence, maintaining control over blood pressure is a vital factor in the management of these patients. In order to determine significant variables associated with changes in SBP over time and assess the effectiveness of classical and machine learning models in predicting SBP, this study aimed to conduct a comparative analysis between the two.*
Methods. *This retrospective cohort study involved the analysis of data from 483 patients with HF who were admitted to Farshchian Heart Center located in Hamadan in the west of Iran, and hospitalized at least two times between October 2015 and July 2019. To predict SBP, we utilized a linear mixed-effects model (LMM) and*

mixed-effects least-square support vector regression (MLS-SVR). The effectiveness of both models was evaluated based on the mean absolute error and root mean squared error.
Results. *The LMM analysis revealed that changes in SBP over time were significantly associated with sex, body mass index (BMI), sodium, time, and history of hypertension (P-value < 0.05). Furthermore, according to the MLS-SVR analysis, the four most important variables in predicting SBP were identified as history of hypertension, sodium, BMI, and triglyceride. In both the training and testing datasets, MLS-SVR outperformed LMM in terms of performance.*
Conclusions. *Based on our results, it appears that MLS-SVR has the potential to serve as a viable alternative to classical longitudinal models for predicting SBP in patients with HF.*

Introduction

Heart failure (HF) is a common, chronic, and complex clinical syndrome [1, 2]. The incidence and prevalence of HF are increasing with aging [3, 4]. The lifetime risk of HF is about 20% [5]. More than 37 million people are suffering from HF worldwide [6]. World Health Organization (WHO) reported that the annual incidence of HF is estimated to be 660,000 per year worldwide. It is expected to be doubled in the next 30 years [7]. About 3.5 % of the Iranian adult population is estimated to be suffering from HF in the future [8].

Blood pressure is a key factor for prognosis in HF patients, easily measured in the patient's examination [9, 10]. Abnormal blood pressure may lead to a worse prognosis in these patients. Several studies have shown that having low or high blood pressure can increase mortality in HF patients [10-14]. Hence, maintaining control over blood pressure is a vital factor in the management of these patients [15]. The reported prevalence of high blood pressure in HF patients was between 25% to 70% in Europe [16] and about 44% in Iran [17]. Furthermore, clinical trials indicate that the risk of HF reduce to nearly 50% by hypertension treatment [18].

Systolic blood pressure (SBP) is strongly indicative of

the prognosis of HF patients [19, 20]. Several studies have shown an association between SBP values with hospitalization and death [10, 21, 22]. Therefore predicting SBP values as a prognostic factor can help reduce readmission and mortality [22]. According to previous studies, SBP values can be changed between visits [23-25]. Therefore, using a longitudinal set of SBP values compared to a single SBP value may increase prognostication accuracy in HF patients [10, 26-28].

There are several models for analyzing data, which are measured at several time points. Linear mixed-effects models (LMM) are common classical models that have been widely used for analyzing these data. However, these models are only able to account for linear relationships between variables [29]. Accordingly, if the relationships between variables are nonlinear, classical models such as LMM may not be useful for data analysis. [30]. To overcome the problem of LMM can be applied to machine learning models [30, 31]. Among them, mixed-effects least-squares support vector regression (MLS-SVR) has been proved to be a very appealing and promising model [32].

In some studies, machine learning models have been used to predict hospitalization and mortality in HF patients [2, 33-35]. However, based on our knowledge,

no studies have assessed longitudinal changes in SBP by machine learning models. Furthermore, evidence on the association of different variables on SBP changes over time in HF patients is still limited. In order to determine significant variables associated with changes in SBP over time and assess the effectiveness of classical and machine learning models in predicting SBP, the objective of this study was to conduct a comparative analysis between the two.

Methods

DATA COLLECTION

This retrospective cohort study involved the analysis of data from 541 patients with HF who were admitted to Farshchian Heart Center located in Hamadan in the west of Iran, and hospitalized at least two times between October 2015 and July 2019. From the initial 541 patients, 58 patients were excluded due to missing at least one of the study variables. Therefore, the analyzes were performed based on a sample of 483 patients. Informed consent was obtained from all patients included in the study. This study was submitted to and approved by the Ethical Committee of Hamadan University of Medical Science (IR.UMSHA.REC.1398.276).

Some of the information regarding patients such as age, sex, body mass index (BMI), history of hypertension (HTN), cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), sodium (Na), and baseline SBP were extracted from medical records. The baseline SBP in each hospitalization was the response variable.

LINEAR MIXED-EFFECTS MODELS (LMM)

The LMM is one of the popular classical models for analyzing continuous longitudinal data. Suppose the denote the longitudinal response of interest, that measured for subject i at time j . An LMM can be expressed as:

$$y_{ij} = \mathbf{w}'\mathbf{x}_{ij} + \mathbf{b}_i'\mathbf{z}_{ij} + \varepsilon_{ij}$$

Here, is a vector of parameters that are associated with fixed effects covariates, is a vector of random effects associated with covariates, and is errors vector from. The are assumed normally distributed with zero mean and covariance matrix and are independent of [29].

MIXED-EFFECTS LEAST-SQUARES SUPPORT VECTOR REGRESSION (MLS-SVR)

The MLS-SVR is one of the appealing machine learning models for analyzing longitudinal data. Let the training dataset be $D = \{(x_{ij}, y_{ij})\}_{ij=1}^{N, n_i}$, where is the j-th response variable of the i-th subject corresponding to fixed-effects covariates. The regression function can be expressed as:

$$y_{ij} = b_0 + \mathbf{w}'\varphi(\mathbf{x}_{ij}) + \mathbf{b}_i'\mathbf{z}_{ij} + \varepsilon_{ij}$$

Here, is a nonlinear feature mapping function, is the bias term, is a vector of random effects covariates with the

random effects parameter, and error vector. For known **B** and the optimization problem of the nonlinear MLS-SVR can be defined as:

$$\min \frac{1}{2}\mathbf{w}'\mathbf{w} + \frac{\lambda_1}{2}\sum_{i=1}^{N}\mathbf{b}_i'\mathbf{B}^{-1}\mathbf{b}_i + \frac{\lambda_2}{2}\sum_{i=1}^{N}\sum_{j,k=1}^{n_i}\varepsilon_{ij}\mathbf{R}_{i\ jk}^{-1}\varepsilon_{ik}$$

subject to equality constraints

$$y_{ij} = b_0 + \mathbf{w}'\varphi(\mathbf{x}_{ij}) + \mathbf{b}_i'\mathbf{z}_{ij} + \varepsilon_{ij}$$

Here, and are tuning or regularization parameters, and is the (j,k) th element of the inverse matrix of, $\mathbf{R}_i, i = 1,...,N, j,k = 1,...,n_i$.

The expression (3) is optimized using the Lagrange function and solving linear equations. Finally, the optimal regression function for a given, expressed as:

$$\hat{y}(\mathbf{x_0}, \mathbf{z_0}) = \hat{b_0} + \sum_{i=1}^{N}\sum_{j=1}^{n_i}\hat{\alpha}_{ij}K(\mathbf{x}_{ij}, \mathbf{x_0}) + \hat{\mathbf{b}}_i'\mathbf{z_0}$$

where are the Lagrange multiplier, and is the kernel function. The Gaussian RBF function is one of the common kernels utilized in this study [32, 36].

VARIABLE IMPORTANCE (VIMP)

In the present study, each variable's importance in predicting SBP was evaluated by a permutation approach with 100 iterations [37]. In each iteration, values of one variable were randomly permuted, and values of other variables were considered constant. Then MAE was calculated for each permutation and the main dataset. Eventually, the mean of differences between MAE for the main dataset and MAE for each permutation was considered as the variable importance (VIMP)[30].

PERFORMANCE CRITERIA

The performance of both LMM and LS-SVR models was assessed in the testing and training dataset. The data were randomly divided into training and testing set with an 70:30 ratio. This procedure was repeated 100 times. The performance of MLS-SVR was compared to LMM via two criteria, which are mean absolute error (MAE) and root mean squared error (RMSE).

Results

This study consisted of 483 HF patients, with 1320 SBP measurements. During the follow-up period, the frequency of hospitalization for these patients was varied between 2 to 5 times. The mean (standard deviation) age of patients at the first hospitalization was 72.06 (13.42) years, majority of the patients were male 318 (65.8 %), and with a history of HTN 276 (57.1 %). The characteristics of the HF patients are given in Table I.

The results of the LMM are presented in Table II. According to the results, sex was significantly related to SBP changes (P = 0.012), which were higher in women. There was a strong association between SBP changes and the history of HTN (P < 0.001). So that the SBP changes were greater in HF patients with a history of

Tab. I. Characteristics of heart failure patients.

Variables	Median	Mean	SD
Age (Year)	73	71.63	13.49
BMI (kg/m²)	28.72	25.92	4.94
Cholesterol (mgr/dl)	163	138.36	40.31
HDL (mgr/dl)	42	36.62	9.55
LDL (mgr/dl)	98	82.10	31.41
Triglyceride (mgr/dl)	131	109.97	40.31
Na (mgr/dl)	141.5	138.77	3.95

BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Na: Sodium, SD: standard deviation.

Tab. II. Linear mixed-effects model analysis for SBP in heart failure patients.

Variables	Coefficient (Standard Error)	P-value
Intercept	-56.05 (22.74)	0.013
Time (Month)	-0.14 (0.06)	0.015
Sex (Female)	4.13 (1.68)	0.014
History of HTN (Yes)	7.68 (1.51)	< 0.001
Age (Year)	0.06 (0.05)	0.286
BMI (kg/m²)	0.40 (0.15)	0.009
Cholesterol (mgr/dl)	0.03 (0.03)	0.220
HDL (mgr/dl)	-0.06 (0.05)	0.245
LDL (mgr/dl)	0.03 (0.03)	0.358
Triglyceride (mgr/dl)	0.01 (0.01)	0.218
Na (mgr/dl)	1.07 (0.16)	< 0.001

SBP: systolic blood pressure, HTN: Hypertension, BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Na: Sodium.

Tab. III. The performance criteria of the models.

Models	Dataset	MAE Mean (SD)	RMSE Mean (SD)
LMM	Training	12.44 (0.28)	16.01 (0.35)
LMM	Testing	17.92 (0.79)	22.79 (0.71)
MLS-SVR	Training	2.21 (0.07)	2.81 (0.10)
MLS-SVR	Testing	17.36 (0.56)	22.07 (0.74)

LMM: Linear mixed-effects model, MLS-SVR: Mixed-effects least-squares support-vector regression, MAE: mean absolute error, RMSE: Root mean squared error, SD: standard deviation.

Fig. 1. VIMP for predicting SBP in heart failure patients.
SBP: Systolic blood pressure, VIMP: Variable importance, HTN: Hypertension, BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Na: Sodium.

reduce mortality and readmission. In the current study, the effects of several variables on SBP changes over time were assessed using classical and machine learning models. The LMM analysis revealed that changes in SBP over time were significantly associated with sex, BMI, Na, time, and history of HTN. Furthermore, according to the MLS-SVR analysis, the four most important variables in predicting SBP were identified as history of HTN, Na, BMI, and triglyceride.

We found a strong association between SBP changes and the history of HTN. So that the SBP changes were greater in HF patients with a history of HTN, the reason may be that these patients might have had a lack of adherence to the use of blood pressure-lowering medicines or an unhealthy diet [38]. Svetkey et al. [39] reported that BP changes were consistently higher in hypertensive than in non-hypertensives.

According to previous studies, there is a close relationship between dietary Na intake and the incidence of hypertension. The reduction in daily Na intake is associated with decreased incidence of hypertension and its morbidity and mortality. A modest reduction in Na intake will cause a fall in blood pressure in a hypertensive and normotensive population. [40]. Also, it has been shown that higher dietary Na intake is strongly related to hospitalization and readmission in patients with chronic HF [41]. The results of our study are in agreement with previous studies because they showed a positive and significant relationship between Na and SBP.

Based on our findings, increased BMI was associated with increased SBP changes. Previous cross-sectional studies have confirmed this result [42, 43]. Ji et al. [44] indicated a greater SBP changes in women compared to men. These findings are also consistent with our results, indicating sex difference in SBP changes over time.

In this study, MLS-SVR identified triglyceride as the fourth important variable for SBP changes in HF patients. However, no significant effect was detected for triglyceride in the LMM model. This may be due to a nonlinear relationship between triglyceride and SBP changes. Previous studies have reported triglyceride as a factor associated with blood

HTN. Also, the variables of BMI and Na were positively associated with the SBP changes, while time was negatively associated with the SBP changes.

The VIMP of the variables obtained from MLS-SVR is shown in Figure 1. According to the MLS-SVR analysis, the four most important variables in predicting SBP were identified as history of HTN, Na, BMI, and triglyceride. Table III shows the performance of LMM and MLS-SVR models to predict SBP in training and testing datasets. As seen, the performance of MLS-SVR compared to LMM was better in both training and testing datasets.

Discussion

One of the important goals for managing HF patients is to control and achieve appropriate blood pressure to

pressure [45, 46]. The association of high triglyceride and systemic HTN has been shown as components of metabolic syndrome and an important contributor to cardiovascular disease in many studies [47].

In the current study, we also compared the performance of classical and machine learning models using cross-validation. According to the results, in both the training and testing datasets, MLS-SVR outperformed LMM in terms of performance. This can be attributed to considering nonlinear and complex relationships between variables by the MLS-SVR model. Therefore, MLS-SVR may be a useful model for predicting SBP in HF patients. Seok et al. [36], in their study, showed that their proposed MLS-SVR model was better than standard models for longitudinal data. In another study, the performance of MLS-SVR was better than LMM, based on two real data and simulation [48]. The results of these two studies were in agreement with our study. In addition, Moghadasi Amiri et al. [30] conducted a comparative study of classical and machine learning models for longitudinal data. They used these models to predict serum creatinine. According to their results, MLS-SVR had the best performance compared to other models, which is consistent with our results.

There are two limitations in this study. First, this was a retrospective study in which some information was missing from patients' records. Second, information regarding the use of HF drugs was not collected. Despite these limitations, this study identified some important variables on SBP changes in HF patients. The results can help cardiologists better control and treat abnormal blood pressure for preventing death and readmission in these patients.

Conclusions

The findings suggest that BMI, Na, and history of HTN were the most important predictors of changes in SBP, as identified by both LMM and MLS-SVR models. Based on our results, it appears that MLS- has the potential to serve as a viable alternative to classical longitudinal models for predicting SBP in HF patients. However, further research is required.

Acknowledgments

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Authors' contributions

RNV and HM contributed to the study design, analysis, and interpretation of data. SKH participated in data collection, data analysis, and writing. JF and AM participated in the interpretations and drafting of the manuscript. All authors read and approved the final manuscript.

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The challenges of urban family physician program over the past decade in Iran: a scoping review and qualitative study with policy-makers

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Keywords

Summary

Introduction. *Despite all the advantages of urban family physician program (UFPP), there is still a gap between UFPP and what is actually achieved by the community after its implementation in Iran. In response, this study attempted to review published studies related to the barriers to the implementation of the UFPP in Iran as well as potential solutions to improve it. Further, a qualitative study was conducted to learn the perspectives of experts at the national level and in the Fars province in order to better understand the program's challenges.*

Methods. *This study was conducted in two phases. First, a scoping review was done, aiming to identify the common barriers and potential solutions to implementing UFPP in Iran. Second, a qualitative study using semi-structured interviews was conducted to investigate the views of decision- and policy-makers regarding barriers to and solutions for implementing the UFPP in the Fars province over the last decade. The findings were classified using the five control knobs framework (organization, financing, payment, regulation, and behavior).*

Results. *The most common barriers to UFPP were: 1) organization (ununited stewardship function of the Ministry of Health, weak management and planning, inadequate training of human resources, and a weak referral system); 2) financing (fragmented insurance funds, insufficient financial resources, and instability of financial resources); 3) payment (inappropriate payment mechanisms and delay in payments); 4) regulation (cumbersome laws and unclear laws); and 5) behavior (cultural problems and conflict of interests). On the other hand, several solutions were identified to improve the implementation of UFPP, including: enhancing the role of government; improving the referral system; providing comprehensive training for UFPP providers; considering sustainable financial resources; moving towards mixed-payment mechanisms; employing appropriate legal and regulatory frameworks; enhancing community awareness; and elevating incentive mechanisms.*

Conclusion. *Our research found that, despite the UFPP having been in place for a decade in Iran, there are still significant challenges in all five components. Therefore, the promotion of this program requires solving the existing implementation challenges in order to achieve the predetermined goals. The ideas in this study can be used to improve the current program in Fars Province and bring it to other cities in Iran.*

Introduction

The World Health Organization (WHO) has defined three goals for health systems: improving populations' health to an acceptable standard, improving the responsiveness of the health care system to legitimate population expectations, and ensuring fairness and equity in financial contribution [1, 2]. According to the WHO's Alma Ata Declaration (1978), implementation of primary health care (PHC) should be prioritized for achieving these goals and strengthening health systems [3]. PHC is regarded as the most inclusive, equitable, and cost-effective way to enable and facilitate access to the packaging of health services (prevention and health promotion, disease treatment and management, and rehabilitation) [4, 5]. PHC should be considered an integral part of any country's health improvement policies because it facilitates the move towards universal health coverage (UHC) [6].

Health systems, in order to increase efficiency and effectiveness, create justice in access to health services, and provide appropriate infrastructure for health service delivery, need to adapt policies and undergo various changes [7]. One of the biggest reforms in health systems is categorizing health care services into three levels, in which the family physician is at the first level [8]. The family physician program (FPP) provides PHC to the population and enables societies to attain UHC [9]. WHO suggests FPP as a key to quality improvement, cost-effectiveness, and equality in the healthcare system [10]. FPP has four principles: delivering PHC to the population, implementing a referral system

through which it is predicted that the population can use specialized services, improving the payment system and protecting people against health costs, and changing the service delivery system from a treatment-oriented to a health-oriented perspective [11]. Family physicians (FPs) are responsible for providing care to individuals and their families and act as gatekeepers [12, 13]. They can make decisions about the appropriate use of health resources, which will reduce health costs and improve health outcomes. FPP, indeed, bridges the gap between people and the health care system to afford efficient and equitable health care services [12, 14].

The FPP and referral system were first developed in the UK in 1985 and were expanded to Europe, Canada, and other countries with significant improvements in healthcare systems as well as justice [15]. Before the Islamic Revolution of Iran in 1979, rural areas were undeveloped and suffered from poor public health indices. Afterwards, by introducing and establishing a health network system based on PHC, the health network system has achieved many improvements because PHC was the solution for many of Iran's health challenges [16, 17]. Gradually, the health system became fragile to respond to the emerging needs of the contemporary population because of the high burden of non-communicable disease, increasing public expectations to access qualified physicians, and the fast growth of expensive technologies [16, 18, 19]. Then the Ministry of Health and Medical Education (MOHME) initiated a series of health sector reforms [20, 21]. FPP in rural areas in 2005 was one of these major reforms that have recently received a lot of attention. FPP was initially introduced in rural areas and small cities with populations of less than 20,000 people [7, 22].

The implementation of this program has resulted in improvements in some of the most important health indicators, including child and maternal mortality rates, life expectancy, and infection disease control [23]. Based on Iran's fifth development program in the health sector and considering the positive effects of rural FP, urban family physician program (UFPP) was implemented as a pilot in two provinces, Fars and Mazandaran, along with referral system instructions to determine the pros and cons of implementing UFPP [24]. This program has attained achievements like out-of-pocket (OOP) payment for medical services, reducing unnecessary referrals to the next specialized level of the health system, and cost-effective use of current health resources. As with rural FPs, UFPs are gatekeepers for managing necessary services in first contact [7, 25, 26].

The establishment of FPP in urban areas versus rural areas had unique differences and complex characteristics that may affect the achievement of the program's desired goal: a passive and fragmented PHC network; a powerful private sector with massive inflict interest among FPs; a public with high freedom in selecting health providers; a tendency of urban residents to visit specialists; and a population with different cultural norms and diversity compared to rural areas. Furthermore, private-sector

specialists are the most powerful stakeholders in health-care providers and do not advocate for FPP-provided preventive services. Hence, there is a gap between FPP and what is actually achieved by the community after its implementation [16, 27-29]. The expansion of this program to other cities depends on the results of the pilot implementation of UFPP in Fars and Mazandaran provinces [24]. Therefore, it is necessary to recognize the main barriers and facilitators of the successful implementation of this program during the last decade to provide a suitable platform for improving its implementation in the coming years. In response, this study attempted to review published studies related to the barriers to the implementation of the UFPP in Iran as well as potential solutions to improve it. Further, a qualitative study was conducted to learn the perspectives of experts at the national level and in the Iranian province of Fars in order to better understand the program's challenges.

Methods

Scoping review methodology

The first part of this study was a scope review that was conducted with the aim of identifying the most common barriers and solutions for the implementation of the UFPP in Iran during the last decade. In order to maximize the reporting quality, the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews (PRISMA-ScR) checklist was used [30]. The main reason for choosing this review methodology was that scoping reviews provide the possibility of bringing together the scientific evidence in a specific field with the aim of answering a broad question. This scoping review was conducted based on the Arksey and O'Malley (2005) guidance [31], which includes five steps: 1) recognizing the research questions; 2) searching and finding the relevant evidence; 3) selecting the studies; 4) charting the collected data; and 5) collating, summarizing, and reporting the findings. The protocol of this study has been reviewed and approved by the Institutional Review Board (IRB) of Shiraz University of Medical Sciences (IR.SUMS.REC.1401.514).

Search strategy

In order to identify the related terms, scanning the Medical Subject Headings (MeSH) thesaurus and contacting relevant experts were applied. Finally, for the search strings, a number of key words, including "family physician," "family physicians," (physicians AND family), and "Iran," were considered. The primary search strategy was established for the PubMed database and then adapted for searching other international journal databases. Electronic databases including PubMed, Scopus, Web of Science, Embase, and ProQuest were searched from January 2012 (the beginning of the UFPP in Fars and Mazandaran Provinces) to September 2022. In addition, Iranian national research databases,

including the Scientific Information Database (SID) and Magiran, were searched with the Persian equivalents of identified key words. To reduce the possibility of publication bias, key journals (Medical Journal of the Islamic Republic of Iran, Archives of Iranian Medicine, Eastern Mediterranean Health Journal, International Journal of Preventive Medicine, Iranian Red Crescent Medical Journal, and BMC Health Services Research) and reference lists of included studies were manually reviewed to identify any missed studies.

SELECTION OF STUDIES

All the search results from both international and national databases were entered into the Endnote X9 software (Clarivate, Philadelphia, USA). After removing duplicates, studies were screened based on title and abstract, and potentially relevant studies were identified for further review based on the full text. Therefore, potential studies were reviewed based on the full text against the inclusion and exclusion criteria, and the final studies were selected. These steps were done by two authors independently, and in case of disagreement, the discussion and participation of the third author were used to resolve it. In this scoping review, all types of studies (quantitative, qualitative, letters to the editor, and opinions) that addressed the challenges of implementing the UFPP in Iran and provided solutions to improve it were considered. However, studies that were conducted on the rural family physician program, review studies, protocol studies, conference studies, and studies without available full text were excluded.

DATA EXTRACTION

The process of getting the needed information was done by three authors on their own, using a form that was made with the help of everyone on the research team. Among the items on this form, the following can be mentioned: 1) first author; 2) publication year; 3) title of study; 4) objective(s); 5) study design; 6) publication language; 7) study population; 8) region; 9) main results; and 10) conclusion. At this stage, any disagreement among the authors was resolved through dialogue and the participation of an expert author.

DATA ANALYSIS

A thematic analysis method was applied to synthesize and structure the results of the included studies [32]. The identified challenges of implementing the family physician program and also potential solutions to improve this program were developed in accordance with the five control knobs framework, including organization, financing, payment, regulation, and behavior [33]. After reviewing and evaluating the differences and similarities among the summaries by the three authors, the sub-themes emerged. The emerging sub-themes, which included challenges and solutions, were then classified and assigned to each component of the five control knobs framework.

Qualitative methodology

PARTICIPANTS

In order to recruit the participants, the research team prepared a list of managers and policymakers related to the UFPP in Fars province and at the national level. Then they were contacted and asked to agree to conduct an interview regarding the challenges of the UFPP and potential solutions for its improvement. After receiving the agreement of the participants to conduct the interview, the informed consent form containing the general information of the study was sent to the participants, and they were asked to express their consent to participate in the study after reading it carefully. In this form, the samples were guaranteed that their identity will remain completely unknown throughout the study, and they can freely withdraw from the study at any stage. In the process of selecting samples, it was tried to consider the maximum diversity in terms of experience and expertise. To cover such diversity, both purposeful and snowball sampling methods were applied.

DATA COLLECTION

Individual semi-structured interviews were used in order to understand the views of the participants in both face-to-face and online formats by two authors (M. H. and F. R.). During the interviews, an interview guide containing open questions was used to better guide the flow of the interview. The main questions in this guide were: 1) Tell us about your experience of implementing the UFPP. 2) If possible, describe the strengths and weaknesses of this program. 3) Which decisions and policies were effective in the implementation process of this program? and 4) As a policymaker, what solutions do you suggest to improve this program and eliminate its weaknesses? Based on the feedback received from the initial interviews, the interview questions were revised and modified for more clarity. After the end of each interview, the recorded audio file was written by the interviewer and saved in Word Office software to facilitate the analysis process.

DATA ANALYSIS

A framework analysis approach was used to analyze the qualitative findings [34]. Three authors (SSH, MH and FZ) did initial coding by repeatedly reading the written texts. Then, the found codes were examined, and the close ones were placed in separate categories. After examining the relationship between the identified categories, they were assigned to the main themes of the study, which are actually the components of the five control knobs framework [33]. In order to minimize bias and maximize the strength of the findings, authors with diverse scientific and executive backgrounds were involved in the analysis process. Also, in cases where there was a lack of agreement among the authors, efforts were made to hold discussion meetings to resolve the lack of agreement, and in the required cases, the participation of an expert author was also used (KBL).

Fig. 1. PRISMA flowchart.
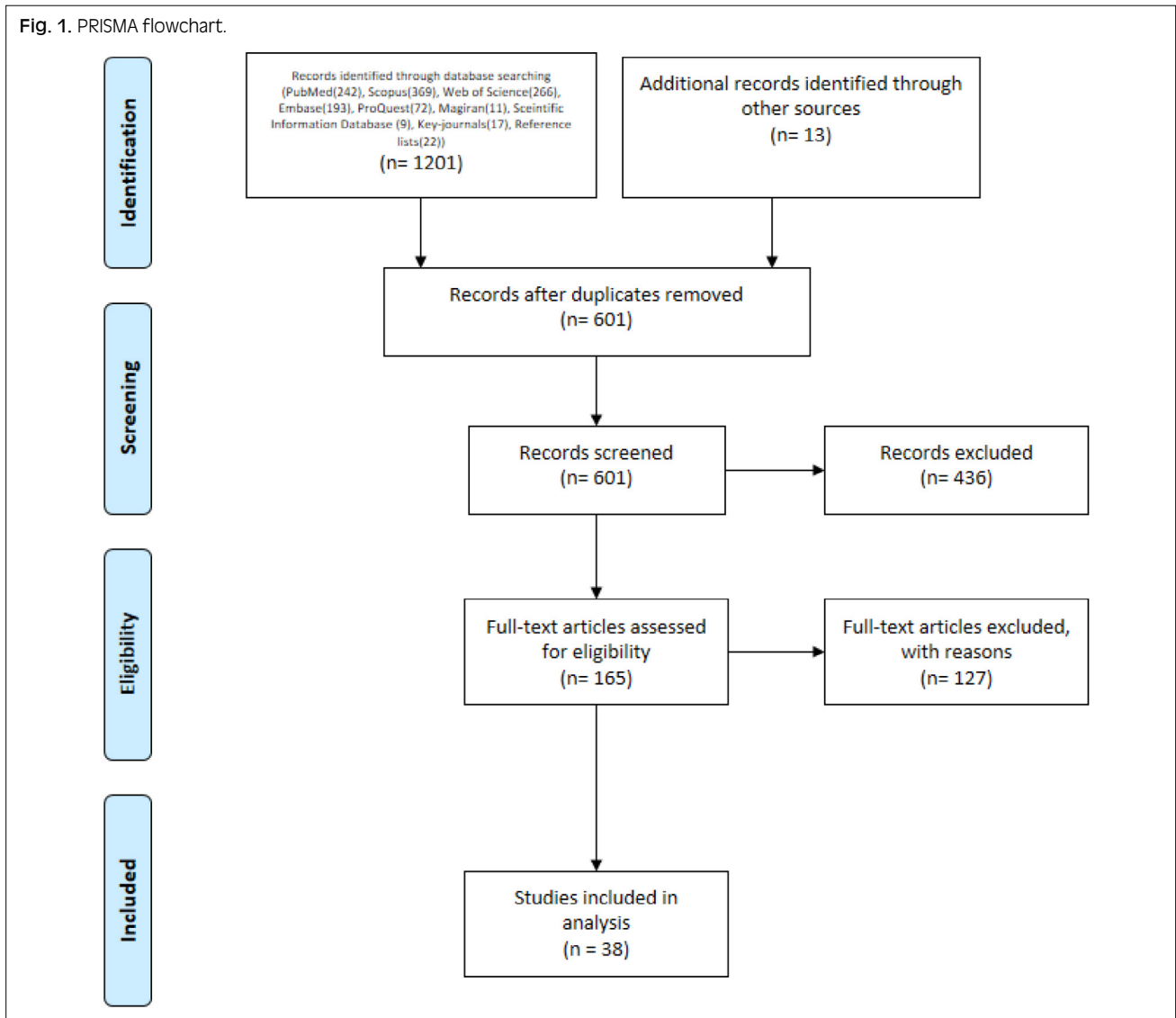
Results

SCOPING REVIEW

Following the initial search, 1214 records were found; after removing duplicates, 601 articles were screened based on the title and abstract. In the next stage, 165 articles were evaluated based on their full texts, and 38 articles were selected as final included studies (Fig. 1) [7, 9, 15, 24, 29, 35-67]. Table I demonstrates the detailed characteristics of the included studies. In the following, the most important challenges of implementing the UFPP and the potential solutions mentioned in the included studies are concisely reviewed.

CHALLENGES

Table II summarizes the challenges of implementing UFFP in Iran based on the studies included. Regarding the organization of UFPP, several challenges have been raised, the most common of which were: 1) weak management and planning; 2) inadequate human resources; 3) inadequate training of human resources; 4) a weak referral system; 5) insufficient physical infrastructure; 6) a high workload; 7) a lack of comprehensive monitoring and evaluation; 8) a weak information infrastructure; and 9) a poor incentive mechanism. Furthermore, a number of the studies mentioned the dispersed stewardship function of the MoHME, poor program notification, insufficient authority of family physicians, unrealistic medical tariffs, frequent turnover of administrators, non-participation of all stakeholders, lack of intra- and inter-sectoral collaboration, office time limits (single work shifts and off weekends), long waiting lists, and inconsistency between community needs and service packages as other organizational challenges.

Several challenges related to UFPP financing have been raised by the studies, which have made its implementation difficult, including: 1) insufficient financial resources; 2) fragmented insurance funds; 3) economic instability; and 4) instability of financial resources. In addition, this scoping review identified a lack of effective fund pooling, an undesirable purchasing system, money

Tab. I. The characterizes of included studies

First author (Year)	Title	Objective(s)	Study design	Publication language	Study population	Region	Main results	Conclusion
Abedi et al. (2017)	SWOT Analysis of Implementation of Urban Family Physician Plan from the Perspective of Beneficiaries	This study aimed at SWOT analysis of urban family physician from the perspective of beneficiaries	Qualitative research	Persian	Nine people including faculty members, family physicians, senior managers and health professionals	National	The main strengths included health services provision, easy accessibility to health services, classification of services, and decrease in unnecessary costs. The weak points according to SWOT analysis included management and planning, human resources, physical resources, referral system, electronic health records, payment mechanism, health services purchasing organizations, inter sectoral coordination, and assessment and control systems. Authorities' support, legal backing, educated human resources, and capacity of private section along public section were identified as the opportunities of the project. Furthermore, failure in public-private sector cooperation, health market and, society needs were considered as the threats	This study showed the strengths and weaknesses of family physician plan, and the opportunities and threats it is faced with. Hence, it is necessary to find solutions and perform necessary interventions in order to eliminate the weaknesses and threats and maintain and improve the strengths and opportunities before its implementation throughout the country
Bagheri Lankarani et al. (2010)	Family physicians in Iran: success despite challenges	NI	Correspondence	English	General population	National	NI	NI
Bayati et al. (2020)	Effect of two major health reforms on health care cost and utilization in Fars Province of Iran: family physician program and health transformation plan	The present study was aimed at evaluating the impact of these two reforms on the level of service utilization and cost of health care services	Interrupted time series	English	People insured by Social Security Insurance Organization	Fars Province	FPP resulted in a significant reduction in the number of specialist visits, imaging, and laboratory tests in the short term, and in the number of radiology services, laboratory tests, and hospitalization in the long term. In contrast, HTP significantly increased the utilization of radiology services and laboratory tests both in the short term and long term. Concerning the costs, FPP resulted in a reduction in costs in short and long term except general practitioners' and specialist visit, and medication in long term. However, HTP resulted in an increase in health care costs in both of the studied time periods	FPP has been successful in rationalizing the utilization of services. On the other hand, HTP has improved people's access to services by increasing the utilization; but it has increased health care costs. Therefore, policymakers must adopt an agenda to revise and re-design the plan
Bayati et al. (2022)	Influencing factors on the tendency of general practitioners to join in urban family physician program	This study aimed to investigate the factors which affect GPs' decision to join in the UFPP	Cross-sectional study	English	666 GPs	National	More than half of GPs (58.6%) participated in the study had a positive tendency to join in the UFPP. Older GPs (adjusted OR = 3.72; 95%CI 1.05-13.09), working in public sector (adjusted OR = 2.26; 95%CI 1.43-3.58), lower income level (adjusted OR = 6.69; 95%CI 2.95-15.16), higher economic expectations (adjusted OR = 2.08; 95%CI 1.19-3.63), and higher satisfaction from medicine profession (adjusted OR = 2.00; 95%CI 1.14-3.51) were the main factors which increased the GPs tendency to enter in UFPP	Decision for joining in the program is mainly affected by GPs' economic status. This clarifies that if the program can make them closer to their target income, they would be more likely to decide for joining in the program
Dehnavieh et al. (2015)	Urban family physician plan in Iran: challenges of implementation in Kerman	This study aims to determine probable implementation challenges of Family Physician Plan in Kerman	Qualitative study	English	21 experts in the field	Kerman	Most prevalent establishment challenges of Family Physician Plan were classified into policy-making, financial supply, laws and resources	The urban Family Physician Plan can be carried out more effectively by implementing this plan step by step, highlighting the relationships between the related organizations, using new payment mechanisms e.g Per Capita, DRG, make national commitment and proper educational programs for providers, development the health electronic Record, justifying providers and community about advantages of this plan, clarifying regulatory status about providers' Duties and most importantly considering a specific funding source

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Delgoshaei et al. (2020)	Performance payment challenges for family physician program	This study aimed to investigate the challenges of implementation of P4P system in family physician program	Qualitative study	English	32 participants including the senior managers with at least 5 years of experience on the family physician program	Tehran	The current study identified 7 themes, 14 subthemes, and 46 items related to the challenges to successful implementation of P4P systems in the family physician program including family physicians' workload, family physician training, promoting family physician program, paying to the family physician team, assessment and monitoring systems, information management, and the level of authority of family physicians	The study results demonstrated notable challenges for successful implementation of P4P system which can helpful to managers and policymakers
Doshmangir et al. (2017)	Infrastructures Required for the Expansion of Family Physician Program to Urban Settings in Iran	This study aimed to explore the major infrastructures perceived to be required to achieve desirable implementation of urban FP through analyzing experts viewpoints reflected in the media and interviews	Qualitative study	English	Relevant and appropriate websites in consultation with some national health expert	National	Infrastructure needed for the implementation of FP were categorized in five main themes and 23 subthemes. The themes are: stewardship/ governance, Actors and stakeholders, structural infrastructure, technical infrastructure and needed resources and information and communication infrastructure	Expansion of FP program to urban settings needs appropriate attention to the principles of policy implementation as well as provision of robust infrastructures. Well-defined stewardship, revised approach to financial regulation and payment system, stakeholder's commitment to collaboration, policy for conflict resolution, and universal insurance coverage are pivotal for expansion of family physician program to the urban settings in Iran
Doshmangir et al. (2018)	Payment system of urban family physician program in the Islamic Republic of Iran: is it appropriate	This study aimed to investigate aspects of the payment system in the urban family physician program(FPP) in the Islamic Republic of Iran	Qualitative study	English	nine key informants from MoHME, two medical universities, insurance companies, and three FPs	NI	A range of concepts was explored related to the payment system of the FPP. By merging similar expressions, we categorized the findings into four main themes including: payment method, payment criteria and incentives, payment process and amount of payment	FPP is required to follow convenient implementation methods. The mechanisms of payment in the health sector are weak and have no transparency. A blurred combination of criteria makes an unclear process for determining the payment mechanisms. It is recommended that the opinions of key stakeholders be taken into consideration prior to developing payment mechanisms and financial incentives
Esmaeili et al. (2016)	The Experience of Risk-Adjusted Capitation Payment for Family Physicians in Iran	This study was conducted with the purpose of exploring the experiences of risk-adjusted capitation payment of urban family physicians in Iran when it comes to providing primary health care (PHC)	Qualitative Study	English	24 family physicians and 5 executive directors	NI	Regarding the effects of risk-adjusted capitation on the primary healthcare setting, five themes with 11 subthemes emerged, including service delivery, institutional structure, financing, people's behavior, and the challenges ahead. Our findings indicated that the health system is enjoying some major changes in the primary healthcare setting through the implementation of risk adjusted capitation payment	With regard to the current challenges in Iran's health system, using risk-adjusted capitation as a primary healthcare payment system can lead to useful changes in the health system's features. However, future research should focus on the development of the risk-adjusted capitation model
Fararouie et al. (2019)	Satisfaction levels with family physician services: a pilot national health program in the Islamic Republic of Iran	This study was conducted in 2014 to measure the rate of user satisfaction with services provided by family physicians to the rural and urban population of the second most populated county in Fars province	Cross sectional	English	160 households	Marvdasht county, Fars province	Overall satisfaction rate was 59.2%: 54.5% for urban areas and 63.2% for rural areas	This study suggests that satisfaction is higher among rural residents and that better quality services from family physicians are needed in both rural and urban communities
Fardid et al. (2019)	Challenges and strengths of implementing urban family physician program in Fars Province, Iran	Family physician (FP) is one of the best strategies to reform health system and Promote population health. Due to the different context, culture, and population, implementing this reform within cities would be more challenging than in rural areas. This study aimed to assess the challenges and strengths of Urban FP Program in Fars Province of Iran	Qualitative study	English	National and regional policy-makers, managers, physicians, health professionals, patients, and members of the public who actively or passively affected the process of decision-making, management, and implementation of UFPP	Fars	The participants' mean age was 44.9 ± 6.4 years, with a mean work experience of 13.2 ± 7.4 years. The transcripts revealed six themes and 17 subthemes. The emerging themes included three challenges and three solutions as following: social problems, financial problems, and structural problems as well as resistance reduction, executive meetings, and surveillance	Resolving staff shortage, decreasing the public resistance, and eliminating unnecessary referrals were among the strategies used by Fars, during FP implementation. To be successful in implementing this program, the required perquisites such as infrastructures and culture growth must be undertaken. The current study suggests the establishment of the electronic health record to improve the pace and quality of service provision as well as reducing violations

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Fardid et al. (2020)	Policy brief on improving the finance of family physician program: An experience from urban areas of Iran Revenue Collection	This policy brief was formulated based on the role of FPs in public access to general practitioner (GP) services in the referral system on one hand, followed by the impact of it on health costs reduction on the another hand, and further considering the necessity of financing system audit to find a sustainable resources for this program to be implemented at a national level in the country of Iran	Policy brief	English	General population	Fars and Mazandaran.	As a result, this policy brief was formulated based on the role of FPs in public access to general practitioner (GP) services in the referral system on one hand, followed by the impact of it on health costs reduction on the another hand, and further considering the necessity of financing system audit to find a sustainable resources for this program to be implemented at a national level in the country of Iran	Paying to midwives from FP's capitation has been designed based on pay for performance. Therefore, detachment of midwives shares from FPs capitation may lead to disobedience of midwives from physicians. So it is suggested that the physician signs a satisfaction certificate for the midwife under supervision prior to payment to her. It will not only make the insurance organizations' payment to midwives uniform but also make the midwives observe job standards and respect to FPs. Besides, training the GPs increases their expectations to receive more rewards and as a result the costs will be increased. Therefore, before training GPs specifically, providing high-quality services by physicians must be assured and the relevant proper evaluation criteria should be set for service receivers
Farzadfar et al. (2017)	Views of managers, health care providers, and clients about problems in implementation of urban family physician program in Iran: A qualitative study	The aim of this study was to determine the viewpoints of managers, providers, and clients of health care services about the problems in the implementation of urban family physician program in Iran	Qualitative study	Persian	Managers, providers, and clients of health care services	Alborz, West Azerbaijan, and Kurdistan Provinces	According to the results of this study, the problems on the implementation of urban family physician program in Iran can be classified into seven categories including: financial, cultural, educational, motivational, structural, administrative, and contextual problems	We propose definition and stabilization of the financial resources and establishment of appropriate rules for payments to solve financial problems, and also training of general population and staffs and involvement of the mass media in training to solve the cultural problems. In order to solve the educational problems reforms in medical curriculum are recommended. Motivational problems can be solved via encouraging the private sector and experts to take part in the program and also through guaranteeing the continuity of the program. Establishment of appropriate organizations and provision of protocols are recommended to solve the structural problems. Finally, to overcome the contextual problems it is suggested to promote cross-sectoral and inter-sectoral coordination and also attract support from policy-makers
Gharibi & Dadgar (2020)	Pay-for-performance challenges in family physician program	This study was conducted to investigate the challenges faced in the implementation of the pay-for performance system in Iran's family physician program	Qualitative	English	32 key informants at the family physician program	Tabriz	This study identified 7 themes, 14 sub-themes, and 46 items related to the challenges in the implementation of pay-for-performance systems in Iran's family physician program. The main themes are: workload, training, program cultivation, payment, assessment and monitoring, information management, and level of authority. Other sub-challenges were also identified	The study results demonstrate some notable challenges faced in the implementation of the pay-for-performance system. This information can be helpful to managers and policymakers
Hajibadal et al. (2022)	Challenges of Implementing Family Physician Program in Urban Communities	This study aimed to explore the challenges and obstacles of implementing family physician program in an Iranian urban community context	Qualitative study	English	19 healthcare recipients and healthcare providers from urban health centers	Bonab	Three main categories including 'socio-cultural and economic challenges', 'interpersonal communication difficulties' and 'inefficient management' emerged as the challenges of implementing urban family physician program in the community	The implementation of family physician program is a long process that is influenced by various factors and elimination of barriers requires developing infrastructures and culture growth and improving the professional settings and interpersonal relationship

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Homaie Rad et al. (2017)	Does Economic Instability Affect Healthcare Provision? Evidence Based on the Urban Family Physician Program in Iran	The main aim of this study was to evaluate the achievements of some important goals of Iran's urban family physician plan. This plan was implemented when the country experienced economic instability. We examine whether an economic crisis affects the efficacy of a healthcare program	Evidence-based	English	NI	Fars	No changes in out-of-pocket payments and healthcare utilization were found after the implementation of this program; however, inequality in out-of-pocket payments increased during the reform	The urban family physician program was not implemented completely and many of its fundamental settings were not conducted because of lack of necessary healthcare infrastructure and budget limitations. Family physician programs should be implemented under a strong healthcare infrastructure and favorable economic conditions
Honarvar et al. (2015)	Knowledge and Practice of People toward their Rights in Urban Family Physician Program	Urban family physician program has been launched as a pilot in Fars and Mazandaran provinces of Iran since 2012. Attitudes of policy makers and people toward urban family physician program have become challenging. This study shows what people know and practice toward this program	Population-Based Study	English	General population	Shiraz	Participation rate was 1257 of 1382 (90.9%), and the mean age of the respondents was 38.1 ± 13.2 years. Of 1257, 634 (50.4%) were men and 882 (70.2%) were married. Peoples' total knowledge toward urban family physician program was 5 ± 2.7 of 19, showed that 1121 (89.2%) had a low level of knowledge. This was correlated positively and in order to being under coverage of this program (P < 0.001), being under coverage of one of the main insurance systems (P = 0.04) and being married (P = 0.002). The mean score of people's practice toward the program was 2.3 ± 0.9 of total score 7, showed that 942 (74%) had poor performance, and it was correlated positively and in order to being under coverage of this program (P < 0.001) and having higher than 1000$ monthly income (P = 0.004). Correlation of people's knowledge and practice toward the program was 24%	Current evidences show a low level of knowledge, poor practice and weak correlation of knowledge-practice of people toward urban family physician program
Honarvar et al. (2016)	Satisfaction and Dissatisfaction Toward Urban Family Physician Program: A Population Based Study in Shiraz, Southern Iran	A national project of extending a family physician program to urban areas has been started since May 2013 in Iran. The present study aimed to detect correlates of people's satisfaction and dissatisfaction about urban family physician program	Population based study	English	General population	Shiraz	Mean age of 1257 participants in the study was 38.1 ± 13.2 years. Respondents included men (634; 50.4%), married (882; 70.2%), those who were educated at universities (529; 42%) and self-employed groups (405; 32.2%). One thousand fifty-eight (84.1%) were covered by the family physician program. Mean of referral times to a family physician was 2.2 ± 2.9 during the year before the study. Satisfaction toward urban family physician program was high in 198 (15.8%), moderate in 394 (31.3%), and low in 391 (31.1%). Dissatisfaction about this program was more among younger than 51-year-old groups (for 31-50 years odds ratio [OR] = 2.3, 95% confidence interval [CI] = 1.4-3.7, P < 0.001 and for 18-30 years OR = 2, 95% CI = 1.2-3.4, P = 0.005), less knowledgeable ones (OR = 2.2, 95% CI = 1.3-3.6, P = 0.001), singles (OR = 2.1, 95% CI = 1.2-3.4, P = 0.003), and those with more than 4 of family members (OR = 1.3, 95% CI = 1-1.7, P = 0.05)	Overall, the majority of the people are not very satisfied with the urban family physician program. This shows the need for a multi-disciplinary approach including training, improvement of infrastructures and referral system, continuous supervision, and frequent monitoring of user's and provider's feedback about this program. According to the results, the family physician program should be improved prior to extending this program to other provinces in Iran

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Honarvar et al. (2018)	Five Years after Implementation of Urban Family Physician Program in Fars Province of Iran: Are People's Knowledge and Practice Satisfactory?	Urban family physician program (UFPP) was launched in Fars province of Iran in 2012. We aimed to assess the knowledge and practice of people toward this 5-year-old program	Population-based study	English	1350 people older than 18 years	Fars	The mean age of the interviewees was 42.4 ± 14.2 years; male (674; 49.9%)-to-female (651; 48.2%) ratio was 1.03. Mean score of knowledge was 4.2 ± 1.7 (out of 14), while 961 (71.1%) had < 50% of the desirable knowledge. Mean score of practice was 4.4 ± 1.3 (out of 9), while only 443 (32.8%) had a good performance toward this program. Knowledge and practice did not show a significant correlation (r = 0.06, P = 0.05). Among cities, the highest and the lowest mean of knowledge belonged to Pasargad (5.6 ± 2.1) and Lar (3.0 ± 1.0) (P < 0.001), respectively. Pasargad (4.8 ± 1.4) had also the highest level of practice compared to Farashband (3.8 ± 1.4) which had the lowest score (P < 0.001). Multivariable analysis showed that supplemental insurance coverage (odds ratio [OR] = 2.5, %95 confidence interval [CI]: 1.6-3.9), female gender (OR = 1.9, %95 CI: 1.2-2.9) and higher level of education (OR = 1.7, %95 CI: 1.1-2.5) were the significant determinants of knowledge, while practice in those who were not covered by supplemental insurance was better (OR = 1.6, 95% CI: 1.2-2.5)	After 5 years of implementation of UFPP, knowledge and practice of people toward UFPP are not satisfactory. This finding calls for a serious revision in some aspects of UFFP
Imanieh et al. (2017)	Factors affecting public dissatisfaction with urban family physician plan: A general population based study in Fars Province	To determine the factors affecting public dissatisfaction with an urban family physician plan in Iran	To determine the factors affecting public dissatisfaction with an urban family physician plan in Iran	English	Family physician plan, specialists, para-clinic services, pharmacy, physicians on shift work, emergency services, and family physician assistants	Fars	In this study, 1,020 individuals (524 males, 496 females) were investigated. Based on the results, the most frequent factor affecting dissatisfaction with physicians was their single work shifts and unavailability (53%). In terms of dissatisfaction with family physicians' specialist colleagues and para-clinic services, the most common factors were related to difficulty in obtaining a referral form (41.5%) and making appointments (21.6%), respectively. Given the level of dissatisfaction with pharmacies, the significant factor was reported to be excessive delay in medication delivery (31.6%); and in terms of physicians on shift work and emergency services, the most important factor was lower work hours for family physicians (9.2%)	It seems that, the most common causes of dissatisfaction with the urban family physician plan are due to the short duration of services, obtaining a referral form and making appointments, and providing prescribed medications
Kabir et al. (2018)	The level of familiarity and attitude of the population covered by the criteria and requirements of the physician program Iranian urban family	This study aims to determine the level of familiarity and attitude of the population It was carried out under the criteria and requirements of the urban family physician program.	Cross-sectional study	Persian	General population	National	Among the 1217 surveyed people, the familiarity level of 551 people(31.1%) from the urban family physician program was low, 695(39.3%) people were average, and 523 people(29.6%) were high. 846 people(56.1%) had a positive attitude and 663 people (43.9%)had a negative attitude towards the criteria and requirements of the program. Eight individual and social variables were influential in the level of familiarity and six variables in the level of people's attitude (P < 0.05).	The results of the study showed that more than 51% of the covered population had a positive attitude and familiarity with the urban family physician program, but some individual variables and Social influence in it

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Kabir et al. (2019)	Family Physicians' satisfaction with factors affecting the dynamism of the urban family physician program in the Fars and Mazandaran provinces of Iran	This study aimed to determine the family physicians' satisfaction level with the factors affecting the dynamism of the urban family physicians program in the Fars and Mazandaran provinces of Iran	Cross-sectional study	English	Physicians	Fars and Mazandaran	The overall satisfaction levels among family physicians in Fars and Mazandaran provinces were 2.77±0.53 and 3.37±0.56, respectively, revealing a statistically significant difference between provinces (p < 0.001). Moreover, the mean satisfaction scores for the performances of healthcare centers, insurance companies, specialists, healthcare workers, and the population covered were 2.78±0.1, 2.54±0.9, 2.52±0.8, 4.24±0.07, and 2.96±0.8, respectively. The family physicians' levels of satisfaction were significantly correlated with population size (p = 0.02, r = -0.106), and willingness to stay in an urban family physician program (p < 0.001, r = +0.398)	This study revealed that family physicians exhibited a low level of satisfaction with the urban family physician program. Given the direct association between family physicians' satisfaction levels and retention in the program, it is expected that family physicians will no longer stay in the program, and it is likely to have subsequent executive problems
Kohpeima Jahromi et al. (2017a)	Continuity of Care Evaluation: The View of Patients and Professionals about Urban Family Physician Program	This study aimed to determine the COC of health care in urban health centers	Cross-sectional study	English	FPs (n = 141) and patients (n = 710)	Fars and Mazandaran	Almost all FPs had a computer. The FPs hadn't kept their patients' medical records routinely. The software had some problems, so the FPs couldn't produce lists of patients based on their health risk and they couldn't monitor their population. Almost 88% of FPs have written referral letters for all referred patients but 57% of them got medical feedback from specialists. About 80% of patients' consultation times were up to 10 min. 29% of FPs knew the past problems and illnesses of the patients. From 40% to 50% of the patients stated that their FPs asked them for their desire about prescribed medicine and gave clear explanation about their illnesses. On average, patients visited their doctor 5.5 times during the previous year. Generally, patients and FPs in Mazandaran could summarize their experiences better than Fars in most topics of COC	It seems that after 3 years of using urban FP program in two pilot provinces, there were still some problems in COC. Strengthen software program, introducing incentives for FPs, and promoting patients' responsibility can be used by policy-makers when they seek to enhance COC
Kohpeima Jahromi et al. (2017b)	Access to Healthcare in Urban Family Physician Reform from Physicians and Patients' Perspective: a survey-based project in two pilot provinces in Iran	The study aimed to access the accessibility of health care in the two pilot sites	Cross-sectional study	English	Family physicians (n = 141) and patients (n = 710)	Fars and Mazandaran	With an average population of 2,332, the main daily task for family physicians was patient visits (n = 39). Most patients were satisfied with the current hours (80%) but visiting a family physician on holidays or after working hours were only rarely possible. The co-payment was an inconvenience to access health services in getting medicines, getting para clinic exams and a visiting specialist. At least 70% of patients could receive their preferred healthcare facilities within 40 minutes. The majority of FPs (64%) believed there were some cultural characteristics in the population that made a limited role for providing better health services	In the reform the providers were geographically well distributed and some features of the organizational access were relatively high. However there were some difficulties in the financial, cultural, and other features of organizational access
Mehrolhas-sani et al. (2021)	Underlying factors and challenges of implementing the urban family physician program in Iran	This study aimed to explain the underlying factors and challenges of implementing the urban family physician program in Iran	Qualitative study	English	44 policy-makers and managers at national and provincial levels	National	A total of 10 categories, 18 sub-categories, and 29 codes were formed. Most challenges related to underlying factors included precipitancy, economic sanctions, belief in traditional medicine, belief in the expertise of previous physicians, and global ranking of countries. For program implementation, most challenges included a diversity of insurance organizations, budget allocation, referral system, electronic file, educational system, and culture building	The major challenges pertaining to underlying factors included international pressure for reforms and precipitancy in program implementation due to management changes. The challenges associated with program implementation included budget provision and interaction with insurance organizations. Therefore, to expand this program to other provinces in Iran, the identified factors should be carefully considered so that sufficient confidence and commitment can be guaranteed for all stakeholders

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Mohammad-ibakhsh et al. (2020)	Family physician model in the health system of selected countries	The purpose of this study is to compare the model of implementation of FPP in the United States, England, Germany, Singapore, Turkey, Egypt, and Iran	Comparative study	English	Family physician	United States, England, Germany, Singapore, Turkey, Egypt, and Iran	In this study, we used the Control Knobs framework to compare countries' FPPs because the framework can demonstrate all necessary features of national health system programs. This framework includes governance and organization, regulation, financing, payment, and behavior in each country. The results of this study show that although the principles of FPP in the selected countries are almost common, they use different methods in FPP implementation	As the success of any policy depends on the political, economic, social, and cultural context of each country, considering these factors and reinforcing each of the control knobs are critical to the success of the family physician's policy implementation	
Nasrollah-pour Shirvani et al. (2013)	Evaluation of the Referral System Situation in Family Physician Program in Northern Provinces of Iran: 2012-2013	This study was performed to evaluate the function of referral system and network system in Northern provinces of Iran	Analytic study	Persian	Patients	Golestan, Mazandaran, Babol and Guilan	From 963 patients who received the level 2 services, 687 cases (71%) were females and 276 (29%) were males. Three hundred and twenty cases (33%) had referral form from health house. Only 299 (31%) persons referred to the centers because of diagnosis of family physician and in 161 (17%) of cases, the family physician had a role to choose a specialist of level 2. For 155 (16.1%) of cases, the specialists wrote the results of their evaluation in feedback form. Only 149 (15.5%) of patients returned to their family physicians. Six hundred ninety-seven (79.6%) of patients did not return to their family physician because of lack of knowledge	The results of this study showed that many principles for referral system from level 1 to higher levels and vice versa are not considered that require education, reformation and intervention in this field	
Ranjbar Eza-tabadi et al. (2015)	Using Conjoint Analysis to Elicit GPs' Preferences for Family Physician Contracts: A Case Study in Iran	This study aimed to elicit GPs' preferences for family physician contracts	Case Study	English	580 GPs selected from the family physician database in Iran	National	The results show that "quotas for admission to specialized courses" is the strongest preference of GPs ($\_$ = 1.123). In order of importance, the other preferences are having the right to provide services outside of the specified package ($\_$ = 0.962), increased number of covered population ($\_$ = 0.814), capitation payment + 15% bonus ($\_$ = 0.644), increased catchment area to 5 km($\_$ = 0.349), and increased length of contract to five years ($\_$ = 0.345)	The conjoint analysis results show that GPs concerned about various factors of family physician contracts. These results can be helpful for policy-makers as they complete the process of creating family physician plans, which can help increase the motivation of GPs to participate in the plan	
Reza Majdza-deh (2012)	Family Physician Implementation and Preventive Medicine; Opportunities and Challenges	NI	Editorial	English	General population	National	There are some challenges in implementing family physician and referral system plan. First is the gap between a plan and its implementation. Second is the deficiency on financial support for the implementation of this plan. Third, medical education in Iran, conventionally, do not prepare trainees appropriately for their future career. Fourth challenge is that health system has not acted as successfully in urban areas as rural. The fifth challenge is the plan's content. The question is that how much family physician plan has been designed according to preventive medicine and public standards	The family physician and referral plan is a promising opportunity for individuals and community health through strengthening public health and preventive medicine services. However, its implementation is seriously challenged, especially in by the financial resources, separation of insurance organization from MOHME, changing utilization behavior of the community and finally service providers who should be enrolled in the plan and provide preventive services	
Sabet Sarves-tani et al. (2017)	Challenges of Family Physician Program in Urban Areas: A Qualitative Research	This study aimed at exploring the challenges of the family physicians program in urban areas in Iran in 2015	Qualitative Research	English	Family physicians	National	Coding and analysis of the interview data generated two categories and seven sub categories related to the challenges of the family physicians program. The categories were poor infrastructure and poor incentive mechanism	Our findings captured a good picture of family physicians program in urban areas to better clarify the challenges of the program and provide a foundation to plan and implement appropriate changes. Thus our findings will give policymakers a deeper perception to confront the challenges of the family physicians program in urban areas	

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Safarpour et al. (2019)	Developing Urban Family Physician Program in Shiraz, Fars Province, the Doctors' Experiences: A Qualitative Research	The purpose of this study was to explain the experiences of urban family physicians in Shiraz, Fars province, Iran	Qualitative study	English	8 physicians in the urban family physician program	Fars	Results were presented in 4 categories: lack of infrastructure, inefficiency of implementation, comprehensive look at the health of the community, and the need for corrective actions along with 17 subcategories	The most important challenges after 8 years of starting a family physician program include the lack of infrastructure, inefficiency of the implementation method, lack of a comprehensive look at the health of the community, and the need for corrective actions in the program. It is the responsibility of health policymakers to address these challenges to improve them. It is recommended that training at all levels of the involved individuals, including theoretical and practical training should be considered
Safizadehe Chamokhtari et al. (2018)	Analysis of the Patient Referral System in Urban Family Physician Program, from Stakeholders' Perspective Using SWOT Approach: A Qualitative Study	The aim of this study was to analyze the patient referral system at all levels of the health system using Strengths, Weaknesses, Opportunities and Threats (SWOT) approach	Qualitative study	Persian	20 people including administrative officers, family physicians, executive managers, and individuals working in insurance sector and 10 people receiving insurance services	National	The strengths included: reducing the costs, providing equitable access to health services, promoting the health level, and providing services in an evolutionary level. The weaknesses included not informing the people, physician issues, poor monitoring and evaluation, management issues, payment mechanisms, electronic health records, insurance organizations, and inadequate facilities and equipment of health centers. Opportunities included: the importance of health and health care for the leadership and the parliament, job creation, active participation of the private sector, the high level of literacy of the target group (people), and the cooperation of insurance organizations. The threats included lack of coordination and alignment between policy makers and planners, the therapeutic focus of health system, lack of attention of people to health care, and the influences of private sector	The appropriate implementation of referral system promotes the health of society and increases the healthcare burden. But today, it does not follow its own rules which is caused by different factors. Therefore, health authorities should address these by appropriate planning and timely actions
Sepehri et al. (2020)	A Descriptive-Comparative Study of Implementation and Performance of Family Physician Program in Iran and Selected Countries	This study aimed to compare the implementation and the performance of FPP in Iran with selected countries, in order to analyze those challenges and suggest potential solutions.	Descriptive-Comparative	English	NI	Iran and six countries (Canada, Australia, United Kingdom, Denmark, United States and the Netherlands)	This study revealed significant differences in implementation of the FPP and relatively low differences in FPP performance between Iran and the selected countries	Implementation and performance of FPP and patient referral system in Iran struggles with serious challenges and burdens, in contrast with the selected reviewed countries. As such, modification of the FPP in Iran seems to be a must. Such modification may include developing educational programs for FPs, clearly defining the duties and practices of FPs, and revising their reimbursement and employment status
Shahabian-moghaddam & Zanganeh Baygi (2022)	Explaining the Role of Physicians in Urban Comprehensive Health Service Centers After Implementing Health Transformation Plan in Southeast of Iran: A Qualitative Study	This study aimed to explain the role of physicians working in urban, comprehensive health service centers after implementing the HTP	Qualitative study	English	Physicians, healthcare providers, managers, and experts, working in urban health centers	Zahedan, Khash, and Saravan	After interviewing 35 people and several stages of review, coding, and using the experience of experts, the data were classified into six main categories, 11 subcategories, and 33 codes. Factors influencing the role of physicians were service delivery, electronic health records, resources, community culture, monitoring, supervision, and practical suggestion. The participants expressed the workload, referral system, integrated electronic health record, financial resources, human resources, equipment, and public participation as some aspects related to the role of physicians	Based on the current study, human and financial resources should be managed to retain the physicians in this plan. In addition, increasing the quality of services, improving electronic health records, and attention to public culture can be considered

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Shiraly et al. (2021)	Doctor-patient communication skills: a survey on knowledge and practice of Iranian family physicians	This study evaluated knowledge and practice of doctor-patient communication among the urban family physicians based on main items of Calgary Cambridge Observation Guides	Cross sectional	English	family physicians	Fars	The study participants included 204 male and 196 female family physicians with a mean age of 46.7 years. The mean communication skills knowledge score was 41.5 (SD: ى 2.8) indicating a high level of knowledge. The mean score for practices was 38.7 (SD: ى 3.4), implying a moderate level of practice. Based on Bloom's scale, nearly 80% of family physicians had good knowledge about doctor-patient communication skills, however, 55% of participants reported moderate to poor level of practice in this regard. Results of multivariate regression analysis suggest that higher levels of related knowledge, having higher age or longer work experience, and working in the public sector can predict better practice scores (P < 0.005)	There is a potential gap between knowledge and self-reported practices toward communication skills among a sample of Iranian family physicians. They have fundamental weakness in the most important evidence based items of doctor-patient communication. Considering significant role of family physicians in prevention and control of non-communicable diseases (NCDs) as an emerging challenge of our country, the topic of communication skills should be inserted as a top educational priority of family physicians
Sokhanvar et al. (2020)	Family physician and referral system adherence in Iranian primary healthcare system	The aim of this study was to investigate the level of adherence of rural insured patients to family physicians (FP) and the referral system, as well as factors that affect self-referral	Cross-sectional study	English	Patients who were referred to select Rural Family Physician Centers (RFPC) during the data collection period	East Azerbaijan Province	Overall, 58.9% of participants adhered to the FPP and referral system. The total self-referral rate was 41.1%, including 24.3% patients who had attended an FP appointment only to obtain a referral code, and 16.8% had self-referred directly. Data on age, sex, family monthly expenditure, and place of residence were associated with self-referral. Structural pitfalls, societal knowledge and attitudes, and cultural challenges were identified as the patients' reasons for self-referring. Within these categories, the most frequent reasons included uncertainty about the knowledge and skills of FPs (74.2%), easy and inexpensive access to specialized services (66.7%), better quality of specialized services (59%), and a lack of awareness of the FPP and the services provided at level 1	A significant percentage of enrollees did not adhere to the FPP and referral system. Considering the unwelcome consequences of self-referral, designing and implementing practical interventions seems essential in order to encourage patients to be more compliant
Tavakoli et al. (2019)	Design of a Model for Management of Referral System in the Iranian Urban Family Physician Program	The purpose of this research was to identify the main dimensions of management of referral systems in family physician program and then introduce them to policymakers of the country primary health care	Describing study	English	Employees of health centers of Mazandaran and Fars Provinces.	Mazandaran and Fars	In confirmatory factor analysis, coefficient of effect of Electronic Health Record on referral system (as the most important dimension), coefficient of Family Physician, coefficient of structure of insurance, coefficient of policymaking in health care system, coefficient of proper stewardship of health system, and basic health care services, were 0.887, 0.877, 0.860, 0.804, 0.568, and 0.522, respectively	Six effective dimensions including Electronic Health Record (as the most important dimension), family physician, structure of insurance, policymaking in health care system, proper stewardship of health sys-tem, and basic health care services were identified. According to six effective dimensions on management model of the referral system in the Iranian urban family physician program, the health system authorities pay serious attention to the six identified dimensions of the current study to improve the health of the urban community
Yazdi Feyz-abadi et al. (2018)	The relationship between the experimental implementation of the urban family physician program and health financial protection indicators in Fars and Mazandaran provinces	The present study was conducted with the aim of investigating the relationship between program implementation and financial protection indicators	Cross-sectional study	Persian	General population	Fars and Mazandaran	The percentage of families faced with Catastrophic health costs increased by 1.82% in the years of program implementation compared to the years before implementation (P < 0/05). This increase was 1.37% for rural areas (P < 0/05). The same percentage of poverty from total health payment increased by 0.83% in the years of implementation of the program. Implementation of the program did not have a significant relationship with Kakuani indicators and direct out-of-pocket payments as a percentage of total health expenses(P > 0/05)	Despite the success of the urban family physician program in increasing physical access to health services, it seems that it has not made significant achievements in improving financial protection and equitable financing of health. However, further studies are necessary.

Tab. II. Challenges of implementation of urban family physician program in Iran (scoping review).

Five control knobs	Challenges	Studies
Organization	Dispersed stewardship function of the MoHME	Doshmangir et al. (2017), Abedi et al. (2017)
	Weak management and planning	Abedi et al. (2017), Dehnavieh et al. (2015), Mehrolhassani et al. (2021), Sabet Sarvestani et al. (2017), Safarpour et al. (2019), Safizadehe Chamokhtari et al. (2018)
	Inadequate human resources	Abedi et al. (2017), Doshmangir et al. (2017), Farzadfar et al. (2017), Hajibadal et al. (2022), Safarpour et al. (2019), Safarpour et al. (2019), Shahabianmoghaddam & Zanganeh Baygi (2022), Sokhanvar et al. (2020)
	Inadequate training of human resources	Bagheri Lankarani et al. (2010), Bayati et al. (2022), Dehnavieh et al. (2015), Delgoshaei et al. (2020), Doshmangir et al. (2017), Farzadfar et al. (2017), Gharibi & Dadgar (2020), Honarvar et al. (2016), Imanieh et al. (2017), Mehrolhassani et al. (2021), Reza Majdzadeh (2012), Safarpour et al. (2019), Safizadehe Chamokhtari et al. (2018), Sepehri et al. (2020), Shahabianmoghaddam & Zanganeh Baygi (2022)
	Weak referral system	Abedi et al. (2017), Doshmangir et al. (2017), Esmaeili et al. (2016), Farzadfar et al. (2017), Honarvar et al. (2016), Imanieh et al. (2017), Mohammadibakhsh et al. (2020), Nasrollahpour Shirvani et al. (2013), Reza Majdzadeh (2012), Sabet Sarvestani et al. (2017), Safarpour et al. (2019), Safizadehe Chamokhtari et al. (2018), Sepehri et al. (2020), Sokhanvar et al. (2020), Yazdi Feyzabadi et al. (2018)
	Insufficient physical infrastructure	Abedi et al. (2017), Dehnavieh et al. (2015), Doshmangir et al. (2017), Farzadfar et al. (2017), Gharibi & Dadgar (2020), Homaie Rad et al. (2017), Mehrolhassani et al. (2021), Sabet Sarvestani et al. (2017), Safarpour et al. (2019), Safarpour et al. (2019), Safizadehe Chamokhtari et al. (2018), Shahabianmoghaddam & Zanganeh Baygi (2022), Yazdi Feyzabadi et al. (2018), Fardid et al. (2020), Imanieh et al. (2017)
	Non-implementation of electronic health record	Abedi et al. (2017), Dehnavieh et al. (2015), Fardid et al. (2019), Kohpeima Jahromi et al. (2017a)
	Non-synchronization of the private and public sector	Abedi et al. (2017)
	High workload	Abedi et al. (2017), Dehnavieh et al. (2015), Delgoshaei et al. (2020), Farzadfar et al. (2017), Gharibi & Dadgar (2020), Kohpeima Jahromi et al. (2017b), Safarpour et al. (2019), Safizadehe Chamokhtari et al. (2018), Shahabianmoghaddam & Zanganeh Baygi (2022)
	Lack of comprehensive monitoring and evaluation	Abedi et al. (2017), Delgoshaei et al. (2020), Farzadfar et al. (2017), Gharibi & Dadgar (2020), Honarvar et al. (2016), Mohammadibakhsh et al. (2020), Safizadehe Chamokhtari et al. (2018), Shahabianmoghaddam & Zanganeh Baygi (2022)
	Poor program notification	Dehnavieh et al. (2015), Farzadfar et al. (2017), Safarpour et al. (2019)
	Inappropriate communication among providers	Dehnavieh et al. (2015)
	Weak information infrastructure	Delgoshaei et al. (2020), Gharibi & Dadgar (2020), Hajibadal et al. (2022), Kohpeima Jahromi et al. (2017a), Mehrolhassani et al. (2021), Yazdi Feyzabadi et al. (2018)Mohammadibakhsh et al. (2020), Safarpour et al. (2019), Safarpour et al. (2019), Safizadehe Chamokhtari et al. (2018), Sokhanvar et al. (2020)
	Insufficient authority of family physicians	Delgoshaei et al. (2020), Gharibi & Dadgar (2020)
	Unrealistic medical tariffs	Doshmangir et al. (2017)
	Frequent turnover of administrators	Doshmangir et al. (2017), Farzadfar et al. (2017), Mehrolhassani et al. (2021)
	Non-participation of all stakeholders	Doshmangir et al. (2017), Fardid et al. (2020), Farzadfar et al. (2017)
	Lack of variation and quality of the services	Fararouie et al. (2019), Hajibadal et al. (2022)
	Fragmented network of primary care	Fardid et al. (2020)
	High freedom in selecting health services	Fardid et al. (2020)
	Gap between theory and practice	Fardid et al. (2020), Reza Majdzadeh (2012)
	Lack of intra- and inter-sectoral collaboration	Farzadfar et al. (2017), Gharibi & Dadgar (2020), Imanieh et al. (2017), Mehrolhassani et al. (2021)

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	Long waiting list	Imanieh et al. (2017), Sokhanvar et al. (2020)
	Office time limit (single work shifts and off weekends)	Imanieh et al. (2017), Kohpeima Jahromi et al. (2017b), Sokhanvar et al. (2020)
	Non-adherence to clinical guidelines	Imanieh et al. (2017)
	Sanctions	Mehrolhassani et al. (2021),
Organization	Poor incentive mechanism	Sabet Sarvestani et al. (2017), Safarpour et al. (2019), Safizadehe Chamokhtari et al. (2018), Shahabianmoghaddam & Zanganeh Baygi (2022)
	Frequent changes in instructions	Shahabianmoghaddam & Zanganeh Baygi (2022)
	Inconsistency between community needs and service package	Shahabianmoghaddam & Zanganeh Baygi (2022)
	Fragmented insurance funds	Abedi et al. (2017), Doshmangir et al. (2017), Fardid et al. (2019), Mehrolhassani et al. (2021)
	Insufficient financial resources	Bagheri Lankarani et al. (2010), Dehnavieh et al. (2015), Delgoshaei et al. (2020), Doshmangir et al. (2017), Farzadfar et al. (2017), Gharibi & Dadgar (2020), Homaie Rad et al. (2017), Mehrolhassani et al. (2021), Reza Majdzadeh (2012)
	Economic instability	Dehnavieh et al. (2015), Hajibadal et al. (2022), Mehrolhassani et al. (2021), Yazdi Feyzabadi et al. (2018)
Financing	Instability of financial resources	Doshmangir et al. (2017), Shahabianmoghaddam & Zanganeh Baygi (2022)
	Lack of effective fund pooling	Doshmangir et al. (2017), Farzadfar et al. (2017)
	Money transfer between budget items	Fardid et al. (2019)
	High costs of services	Imanieh et al. (2017)
	Undesirable purchasing system	Mehrolhassani et al. (2021)
	Soaring expenses	Sabet Sarvestani et al. (2017)
	Imposing additional Costs	Safarpour et al. (2019)
	Insufficient service compensation	Abedi et al. (2017), Hajibadal et al. (2022), Sepehri et al. (2020)
	Inappropriate payment mechanism	Abedi et al. (2017), Dehnavieh et al. (2015), Doshmangir et al. (2018), Sabet Sarvestani et al. (2017), Safizadehe Chamokhtari et al. (2018), Shahabianmoghaddam & Zanganeh Baygi (2022)
Payment	Delay in payments	Abedi et al. (2017), Dehnavieh et al. (2015), Doshmangir et al. (2017), Fardid et al. (2019), Farzadfar et al. (2017), Safizadehe Chamokhtari et al. (2018)
	Lack of outcome-based payment	Abedi et al. (2017), Delgoshaei et al. (2020)
	Considering co-payment for users	Kohpeima Jahromi et al. (2017b)
	Cumbersome laws	Dehnavieh et al. (2015)
Regulation	Unclear rules	Dehnavieh et al. (2015), Farzadfar et al. (2017)
	Law deviation	Fardid et al. (2019)
	Absence of legal requirements	Safizadehe Chamokhtari et al. (2018)
	Cultural problems of service users	Dehnavieh et al. (2015), Delgoshaei et al. (2020), Farzadfar et al. (2017), Kohpeima Jahromi et al. (2017b), Mehrolhassani et al. (2021), Safizadehe Chamokhtari et al. (2018)
	Cultural problems of providers	Dehnavieh et al. (2015)
	Conflict of interests	Dehnavieh et al. (2015), Fardid et al. (2020), Farzadfar et al. (2017), Mohammadibakhsh et al. (2020), Reza Majdzadeh (2012), Safarpour et al. (2019)
	Low incentives of physicians to work in deprived areas	Dehnavieh et al. (2015), Kabir et al. (2019)
	Service providers' concerns regarding funding	Dehnavieh et al. (2015), Farzadfar et al. (2017), Ranjbar Ezatabadi et al. (2015)
Behavior	Lack of awareness among people	Delgoshaei et al. (2020), Fardid et al. (2019), Farzadfar et al. (2017), Farzadfar et al. (2017), Gharibi & Dadgar (2020), Honarvar et al. (2015), Honarvar et al. (2018), Kabir et al. (2018), Sabet Sarvestani et al. (2017), Safizadehe Chamokhtari et al. (2018), Shahabianmoghaddam & Zanganeh Baygi (2022)
	Patients' preferences (for visiting by specialists)	Esmaeili et al. (2016), Fardid et al. (2020), Mehrolhassani et al. (2021), Sokhanvar et al. (2020)
	Inappropriate behavior of staff	Fararouie et al. (2019), Imanieh et al. (2017)
	Discrimination	Fardid et al. (2019)
	Resistance against implementation	Fardid et al. (2019)

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Behavior	Treatment-centered advertisements by mass media	Fardid et al. (2020)
	Adherence to the indigenous norms	Hajibadal et al. (2022), Mehrolhassani et al. (2021)
	Lack of proper communication between the healthcare provider and the patient	Hajibadal et al. (2022), Kohpeima Jahromi et al. (2017a), Shahabianmoghaddam & Zanganeh Baygi (2022), Shiraly et al. (2021), Yazdi Feyzabadi et al. (2018)
	Lack of trust in health care providers' competencies	Hajibadal et al. (2022)
	Physicians' dissatisfaction	Kabir et al. (2019)
	Lack of acculturation	Sabet Sarvestani et al. (2017)
	Egoistic manner of medical specialists	Sabet Sarvestani et al. (2017), Safarpour et al. (2019),
	Lack of awareness among GPs	Sokhanvar et al. (2020)

transfers between budget items, and soaring expenses as other financing barriers to implementing UFPP. Notably, a large proportion of included studies raised concerns about the UFPP payment system, such as insufficient service compensation, ineffective payment mechanisms, payment delays, a lack of outcome-based payment, and the consideration of co-payment for users.

Cumbersome laws, unclear rules, law deviations, and the absence of legal requirements were the most commonly identified regulatory barriers in implementing the UFPP, as reported in the included studies. Furthermore, the current review identified a wide range of challenges related to the fifth dimension of the adapted framework, namely behavior. Among others, 1) cultural problems of service users; 2) conflict of interests; 3) lack of awareness among people; 4) patients' preferences; 5) lack of proper communication between the healthcare provider and the patient; and 6) the egoistic manner of medical specialists were expressed by more studies. Nonetheless, other behavior-related challenges were: low incentives for physicians to work in deprived areas; service providers' concerns regarding funding; inappropriate behavior of staff; adherence to indigenous norms; and a lack of trust in health care providers' competencies.

SOLUTIONS

Even though there are a lot of problems with how the UFPP is being carried out in Iran, the included studies that were looked at also came up with a number of ways to improve this (Tab. III is a summary of these solutions). Specifically, most of the solutions were related to the organization component. In this regard, the most common solutions were: 1) multi-dimensional planning; 2) promoting referral systems; 3) comprehensive training courses for providers; 4) establishing continuous professional development programs; 5) establishing electronic health records; 6) considering sufficient workforce resources; 7) creating appropriate monitoring and supervision systems; 8) creating an effective information system; 9) preparing protocols and guidelines; 10) enhancing intra- and inter-sectoral collaborations; 11) developing infrastructures; and 12) administering the centers through work shifts. In addition, enhancing the role of government, facilitating good interaction among beneficiaries, involving the mass media, clarifying the role of involved professionals,

granting a reasonable level of authority to family physicians, and increasing the number of workforces were the other proposed solutions to improve the organization of the UFPP in Iran.

A number of the included studies proposed that considering a sustainable financial resource is essential to enhancing the financing of UFPP in Iran. Furthermore, merging the insurance funds, considering an extra fund, assigning franchises, creating an integrated virtual fund, and provider–purchaser separation were other identified solutions to improve the financing dimension of this program. Regarding the payment system, a significant number of studies concluded that there was a need to improve the payment system for UFPP employees. In addition, they reported that using risk-adjusted capitation mechanisms, moving toward the Beveridge family payment model, and considering a detachment of physician capitation from health care providers could be other potential solutions to strengthen the payment system. Through this scoping review, several policies were recognized to promote the regulation component of UFPP, including: 1) employing appropriate legal and regulatory frameworks; 2) constant reviewing of policies, rules, and regulations; and 3) applying efficient strategies by the government to encourage relevant stakeholders to join the program. In the final report, several recommendations were identified to curb the behavior-related challenges of UFPP in Iran, of which the most common were: enhancing community awareness, promoting public culture for using FP services, and improving the clinical knowledge of the population. Furthermore, strengthening the economic status of providers, considering incentives to attract workforces, using scientific evidence by providers, promoting patients' responsibility, considering the concerns of providers, and enhancing the communication skills of physicians were other potential solutions.

QUALITATIVE INTERVIEWS

Tables IV and V summarize the extracted challenges and solutions from the 15 participants' interviews. Among the participants, one was a former deputy of the MoHME, three were senior policymakers and planners of the family physician program in the MoHME, one was a former deputy of the Program and Budget Organization, two were former chancellors of Shiraz University of

Tab. III. Solutions to improve the implementation of urban family physician program in Iran (scoping review).

Five control knobs	Solutions	Studies
Organization	Enhancing the role of government	Bayati et al. (2022), Mohammadibakhsh et al. (2020)
	Multi-dimensional planning	Honarvar et al. (2015), Honarvar et al. (2016), Mohammadibakhsh et al. (2020)
	Seeking advocacy from political groups	Delgoshaei et al. (2020)
	Step-by-step implementation	Safarpour et al. (2019)
	Constant reviewing policies, rules, and regulation	Dehnavieh et al. (2015)
	Promoting referral system	Fardid et al. (2019), Imanieh et al. (2017), Kohpeima Jahromi et al. (2017b), Mehrolhassani et al. (2021), Reza Majdzadeh (2012), Safizadehe Chamokhtari et al. (2018), Sepehri et al. (2020), Shahabianmoghaddam & Zanganeh Baygi (2022), Sokhanvar et al. (2020)
	Comprehensive training course for providers	Bagheri Lankarani et al. (2010), Fardid et al. (2020) Farzadfar et al. (2017), Gharibi & Dadgar (2020), Honarvar et al. (2015), Sepehri et al. (2020), Shahabianmoghaddam & Zanganeh Baygi (2022)
	Continuous professional development program	Bagheri Lankarani et al. (2010), Honarvar et al. (2015), Imanieh et al. (2017), Kohpeima Jahromi et al. (2017a)
	Establishing electronic health record	Fardid et al. (2019), Imanieh et al. (2017), Mehrolhassani et al. (2021), Shahabianmoghaddam & Zanganeh Baygi (2022), Sokhanvar et al. (2020)
	Using internet-based virtual learning	Bagheri Lankarani et al. (2010)
	Engaging private sector	Farzadfar et al. (2017), Mohammadibakhsh et al. (2020)
	Considering specialty training for family physicians	Bagheri Lankarani et al. (2010), Sokhanvar et al. (2020)
	Considering sufficient workforce resources	Dehnavieh et al. (2015), Shahabianmoghaddam & Zanganeh Baygi (2022)
	Creating appropriate monitoring and supervision systems	Dehnavieh et al. (2015), Delgoshaei et al. (2020), Fardid et al. (2019), Gharibi & Dadgar (2020), Honarvar et al. (2015), Imanieh et al. (2017), Imanieh et al. (2017), Mohammadibakhsh et al. (2020), Sabet Sarvestani et al. (2017), Shahabianmoghaddam & Zanganeh Baygi (2022)
	Enhancing the quality of services	Fararouie et al. (2019)
	Facilitating good interaction among beneficiaries	Dehnavieh et al. (2015), Gharibi & Dadgar (2020)
	Establishing an appropriate working culture	Dehnavieh et al. (2015),
	Involvement of mass media	Dehnavieh et al. (2015), Farzadfar et al. (2017)
	Determining the physicians' workload	Delgoshaei et al. (2020)
	Improving management skills of providers	Delgoshaei et al. (2020)
	Creating effective information system (qualified registry system)	Delgoshaei et al. (2020), Gharibi & Dadgar (2020), Honarvar et al. (2016), Imanieh et al. (2017), Kohpeima Jahromi et al. (2017a), Sokhanvar et al. (2020)
	Clarifying the role of involved professionals	Delgoshaei et al. (2020), Gharibi & Dadgar (2020)
	Applying outcomes-focused approach	Delgoshaei et al. (2020)
	Preparing protocols and guidelines	Farzadfar et al. (2017), Gharibi & Dadgar (2020), Sokhanvar et al. (2020)
	Enhancing intra- and inter sectoral collaborations	Farzadfar et al. (2017), Gharibi & Dadgar (2020), Gharibi & Dadgar (2020), Hajibadal et al. (2022), Imanieh et al. (2017), Mehrolhassani et al. (2021),
	Clarifying the responsibilities	Gharibi & Dadgar (2020)
	Granting a reasonable level of authority to family physicians	Gharibi & Dadgar (2020), Delgoshaei et al. (2020)
	Developing infrastructures	Hajibadal et al. (2022), Homaie Rad et al. (2017), Mohammadibakhsh et al. (2020), Shahabianmoghaddam & Zanganeh Baygi (2022)
	Implementation of the program at the time of economic stability	Homaie Rad et al. (2017)
	Increasing the number of workforces	Imanieh et al. (2017), Kohpeima Jahromi et al. (2017b
	Administering the centers through work shifts	Imanieh et al. (2017), Kohpeima Jahromi et al. (2017b), Sepehri et al. (2020)
	Representatives of family physicians for decision making	Safarpour et al. (2019)

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Organization	Institutionalizing the gatekeeper role for FPs	Sepehri et al. (2020)
Financing	Considering a sustainable financial resource	Dehnavieh et al. (2015), Farzadfar et al. (2017), Mehrolhassani et al. (2021), Mohammadibakhsh et al. (2020), Shahabianmoghaddam & Zanganeh Baygi (2022)
	Merging the insurance funds	Fardid et al. (2019)
	Considering an extra fund	Fardid et al. (2020)
	Assigning franchises	Fardid et al. (2020)
	Creating an integrated virtual fund	Fardid et al. (2020)
	Provider–purchaser separation	Mohammadibakhsh et al. (2020)
Payment	Improving payment system	Dehnavieh et al. (2015), Delgoshaei et al. (2020), Doshmangir et al. (2018), Farzadfar et al. (2017), Kohpeima Jahromi et al. (2017a), Mohammadibakhsh et al. (2020), Sokhanvar et al. (2020)
	Using risk-adjusted capitation mechanism	Esmaeili et al. (2016), Gharibi & Dadgar (2020)
	Moving toward the Beveridge family payment model	Fardid et al. (2020)
	A detachment of physician capitation from health care providers	Fardid et al. (2020)
Regulation	Employing appropriate legal and regulatory frameworks	Sepehri et al. (2020)
	Constant reviewing policies, rules, and regulation	Dehnavieh et al. (2015)
	Applying efficient strategies by government to encourage relevant stakeholders for joining in the program	Bayati et al. (2022)
Behavior	Strengthening economic status of providers	Bayati et al. (2022)
	Improving the clinical knowledge of the population	Doshmangir et al. (2018), Farzadfar et al. (2017)
	Enhancing community awareness	Fardid et al. (2019), Gharibi & Dadgar (2020), Honarvar et al. (2015), Honarvar et al. (2018), Kabir et al. (2018), Kabir et al. (2019)
	Promoting public culture for using FP services	Fardid et al. (2019), Fardid et al. (2020), Hajibadal et al. (2022), Kabir et al. (2019)
	Considering incentives to attract workforces	Fardid et al. (2019),
	Using scientific evidence by providers	Imanieh et al. (2017)
	Promoting patients' responsibility	Kohpeima Jahromi et al. (2017a)
	Incentive programs for FPs who teach their populations in prevention programs	Kohpeima Jahromi et al. (2017b)
	Considering the concerns of providers	Ranjbar Ezatabadi et al. (2015)
	Using rotational shifts	Safarpour et al. (2019)
	Receiving franchise to reducing induced demands	Safarpour et al. (2019)
	Enhancing communication skills of physicians	Shiraly et al. (2021)

Medical Sciences, two were former vice chancellors of Shiraz University of Medical Sciences, the former president of health insurance in Fars Province, three were senior officials of the family physician program in Fars Province, and two were people from the Medical Council of the Islamic Republic of Iran were also participants. Qualitative findings have been detailed in the Supplemental file 1.

Discussion

According to the current study, the UFPP faces five dimensions of challenges: organization (distributed stewardship, high provider workload, inadequate human resource training, weak referral systems, lack of comprehensive monitoring and evaluation, poor information infrastructure, inappropriate management and planning, and lack of intra- and inter-sectoral collaboration); financing (insufficient financial resources, fragmented insurance, and instability of financial resources); payment (inappropriate payment mechanism, delay in payments, and lack of outcome-based payment); regulation (cumbersome laws, unclear rules, and absence of legal requirements); and behavior (cultural problems, conflict of interests, lack of proper

communication between the healthcare provider and the patient and lack of determination and incentive). However, a number of solutions were also found in order to improve the implementation of this program all over the country and especially in the Fars province.

Organization

Stewardship, including intra-sectoral governance and inter-sectoral leadership, plays a very important role in the successful implementation of a program, especially for programs that have different stakeholders [68, 69]. In this study, it was shown that the lack of united stewardship caused the implementation of the UFPP to face a serious challenge. In Iran, the role of the MoHME has indeed shifted from policymaking and supervision to financing and providing healthcare services, which has made it unable to fulfill its governance and leadership roles in a desirable manner [70, 71]. Therefore, it is necessary for the MoHME to return to its main functions, such as policymaking and supervision, in order to provide the necessary platform to guide reform programs, including UFPP [29, 39].

This study identified that, in addition to the inadequate human resources of the UFPP, the existing workforces also do not have enough knowledge and skills to work on this project. In fact, the lack of community-oriented training and the lack of a holistic view among the involved professions have caused them to lack sufficient preparation to provide family physician services [23, 39]. Indeed, focusing on treatment-oriented courses in the educational system has made it difficult for practitioners to understand health-oriented problems [54]. Thus, many studies have suggested that we should train appropriate practitioners and therapists for community-oriented programs such as family physicians by making amendments to educational curricula [29, 36, 61]. In addition, ad hoc training and constant educational courses should be considered seriously in order to update knowledge and skills [23].

The weakness of referral system has always been recognized as one of the obstacles to the effective implementation of the UFPP in Iran. The referral system allows people to access facilities and health services based on their needs and priorities [59]. In this regard, in the law of the fifth development plan, the creation of an effective referral system is emphasized as a mandatory law by the MoHME. However, with the passing of several years under such a law, the health care referral system in Iran is facing serious challenges that have greatly affected the UFPP. Various factors have led to the emergence of such a situation, including easy access to specialized services, a lack of an accurate information system, a lack of awareness about UFPP goals, cultural problems, etc. [21, 44, 72]. Nonetheless, evidence suggests that family physicians acting as gatekeepers can reduce costs and improve care quality [60, 73]. Therefore, strengthening the referral system through increased cooperation between different levels of the

health care system, cooperation between the public and private sectors, and the creation of accurate information systems is a vital prerequisite for the successful implementation of the UFPP [44, 49, 53].

Insufficient physical and information infrastructures were other identified challenges that mentioned by other studies [35, 39, 74]. Although a decade has passed since the implementation of the UFPP, there are still problems with physical space and equipment. In addition, the inappropriateness of the information infrastructure, such as the unavailability of electronic health records, has caused the professions involved in the UFPP to not perform well [40, 46, 54]. Even though in 2016, a national action was taken to develop an integrated health system for Iranians by creating an electronic health record registration system, this problem has not yet been fully resolved [54]. Therefore, besides the development of physical infrastructure, the successful implementation of the UFPP requires the development of software infrastructure with the aim of accessing people's health records.

Lack of comprehensive monitoring and evaluation was another challenge identified through this study. Indeed, performance evaluation allows decision- and policy-makers to amend and modify paths based on the variables involved [23]. Although checklists were developed to monitor and evaluate the services provided by the UFPP team, the feedback obtained from them has not been effectively used to improve policies and service delivery processes [75]. In response, a number of studies have emphasized the importance of effective monitoring and evaluation in order to minimize the drawbacks of programs [45, 59, 61]. Therefore, it is crucial to develop effective monitoring and evaluation systems both at the individual and team level while recognizing the existing deficiencies and modifying the policies in order to strengthen the UFPP services.

High workload, along with the lack of sufficient incentive mechanisms, has caused the performance of UFPP providers to be significantly affected. Related evidence has also revealed that physicians and other health care providers in the family physician program are unhappy with the high workload and low pay [23, 39, 58]. Notably, family physician facilities differ greatly between developed and underdeveloped areas [25]. This has made many physicians reluctant to participate in the program, especially in less developed areas. Moreover, the presence of a significant share of physicians and health care workers in the UFPP is not permanent, which has caused them to not enjoy job stability [23]. In addition, some studies have indicated that family physicians suffer from mental disorders (like stress and burnout) and job dissatisfaction due to inappropriate financial compensation, a high workload, and inadequate time to balance their personal lives with their professional lives [23]. Thus, by applying a wide range of strategies while reducing the workload of the providers, it is necessary to move in the direction of increasing their motivation to participate in UFPP.

Tab. IV. Challenges of implementation of urban family physician program in Iran (qualitative study).

Five control knobs	Categories	Codes	Participant ID
Organization	Dispersed stewardship	The stewardship function of the MoHME had been dispersed with its inadequate authority to implement the FP program.	Participant 01
		The lack of justification of the political and executive authorities or the insufficient information provided	Participant 06
		Weak governance in Iran's health system and instability in policies lead to the implementation of UFPP was not successful	Participant 02
		Lack of integrity to provide health care in Iran's health system	Participant 01
	High workload of family physician	The ratio of physicians to the population in Mazandaran province was inadequate, also considering the workload and responsibilities of the urban family physician.	Participant 01
		The working hours of UFPP* were from morning until evening, due to the high volume of visits. Also, the bureaucracy dramatically increased the workload.	Participant 02
		One of the problems faced by family physicians was the lack of annual or monthly leave and high working responsibility.	Participant 01
	Lack of comprehensive education	There were insufficient skills and training levels in family physicians to better implement this plan.	Participant 01
		The lack of a community-based vision in the educational system, and the lack of involvement of the members of the health team in the family physician's education system.	Participant 01
		Inadequate skills and training for service providers and lack of retraining programs.	Participant 01
		The medical education in Iran, conventionally, do not prepare trainees appropriately for their future career.	Participant 01 Participant 03
		The non-readiness of physicians for caregiving as an FP and lack of experience, as well as lack of a holistic view of this program, was problems to the fully effective implementation of UFPP.	Participant 01
	Inadequate workforces	The number of trained physicians, caregivers, and midwives was not proportional to the population covered.	Participant 04 Participant 05
	Weak referral system	There is no systematic referral system in Iran's health system. Therefore, there is no restriction on access to specialist levels and hospitals. This is despite the fact that an effective referral system prevents unnecessary visits to more specialized levels as well as the waste of material and human resources.	Participant 01
		No one cares about the second-level referral cycle and hospitals are only concerned with making money and paying their bills. Although the referral system is a good tool for controlling healthcare costs and increasing the standardization of clinical practices between general practitioners and specialists.	Participant 01
		The second-level referral was not well defined and there were limitations in referral to secondary care.	Participant 06
		One of the reasons for the ineffectiveness of the program was the optional referral system.	Participant 05
	Lack of effective monitoring and evaluation Inadequate incentive mechanism	There was a poor monitoring and evaluation system in Iran's health system to assess the performance of service providers.	Participant 01
		There was no accreditation evaluation system for urban family physicians.	Participant 02
		Output indicators and Outcome indicators were not approved for UFPP evaluation.	Participant 04
		In the UFFP the supervisions are mostly quantitative, and qualitative supervision has not been done.	Participant 05
		Most doctors only practiced as family physicians when they had no choice.	Participant 01
		Inadequate remuneration and denigration of family physicians and also, inadequate remuneration for midwives were the reasons for the failure of the program.	Participant 03 Participant 05 Participant 07
		Unreasonable facilities in the residence, inappropriate work environment, and insufficient equipment and medical facilities have contributed to the lack of motivation of family physicians.	Participant 06

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Organization	Lack of effective monitoring and evaluation Inadequate incentive mechanism	The specialist incentives for further collaborations have gradually diminished over time and lack of motivation is one of the main barriers to providing effective health services	Participant 01
		Unsuitable salary requirements, lack of job security, and lack of opportunity for continuing education were regarded as the most common reasons for leaving the program.	Participant 02
		Failure to prepare and attract the cooperation of the media.	Participant 06
	Lack of comprehensive information system	Lack of electronic health database of individuals and suitable infrastructure for the development of the health information system.	Participant 01 Participant 05 Participant 06 Participant 07 Participant 08
		There is currently no comprehensive and proper electronic record in Iran and different levels of the health system are not linked to it.	Participant 01 Participant 05 Participant 06
		Inadequate amount of information sent from referral sources to hospitals and vice versa.	Participant 06
	Administrative issues	Changes in management and policies easily influence the plan's progress.	Participant 02
		The therapeutic focus of the UFPP caused soaring expenses and reduced achievement.	Participant 01 Participant 08
		There was a gap between a UFPP plan and its implementation.	Participant 02
		At the beginning of the implementation of the UFPP, service packages were not defined.	Participant 01
		To follow up on the patient's health by the family physician a service package was not defined.	Participant 04 Participant 06
		National planning meetings are not held in the executive headquarters of the UFPP, and most importantly, the stakeholders are not present in these meetings.	Participant 01
		The national headquarters, which should have existed in the MoHME and followed up the program, was closed.	Participant 02
		The coordination meetings of the National Family Physician staff and its executive staff have not been held due to inadequate management and political commitment.	Participant 04
		There was no political interest in the process of implementing the UFPP.	Participant 03 Participant 07
		There was no responsibility commensurate with authority in the UFPP.	Participant 04
		The implementation of UFPP was done at the micro level without coordination with the macro level.	Participant 04
		In addition to the role of health management, the family physician should also be given the role of financial management.	Participant 04
		The UFPP in Iran should have been implemented nationally and not on a pilot basis. Because it caused inertia in service recipients.	Participant 04 Participant 05
		In the implementation of the UFPP, we did not see all the axes and our view was not systemic and holistic.	Participant 04
		In UFPP, the important role of the family physician in prevention and health promotion was ignored.	Participant 06 Participant 08
		The pharmaceutical communication between the family physician and the pharmacy was not good. Pharmacies complained about the payments.	Participant 06
		They did not determine the per capita correctly and logically.	Participant 05 Participant 07
		The main goals of the program, which were risk assessment and health improvement, have not been achieved because the family physician and midwives, and caregivers were not provided with a suitable platform.	Participant 03
		Not using the points of view of the main owners of this program (family physicians and associations of general practitioners and executives) was another factor in the failure of the program.	Participant 07
	Insufficient Intra- and sector collaboration	The weakness of inter-sector collaboration and people's participation affected the fully effective implementation of UFPP.	Participant 01

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Organization	Insufficient Intra- and sector collaboration	Failure in public-private sector cooperation in particular in the Fars province due to a large number of private clinics and the conflict of interest with their capitalists. (Mazandaran province had better public-private sector cooperation).	Participant 01 Participant 07
		Not participation of all stakeholders was another factor in the failure of the program.	Participant 06
		The lack of coordination between the Ministries of Health and Welfare created confusion and problems for both providers and recipients of services and the insurance system.	Participant 06
Financing	Budget deficits	Following the implementation of UFPP in 2013, financing has been provided through the public budget, which was funded by the Ministry of Health and Medical Education (MoHME) and the Ministry of Cooperatives, Labor, and Social Welfare (MoCLSW). Therefore, a suitable budget was allocated at the beginning of the UFPP and Over time, financial problems have caused delays in payments to service providers.	Participant 01 Participant 02
		Not having sustainable financing in the budget line for UFPP.	Participant 01 Participant 03 Participant 06
		The budget required for the UFPP was foreseen and approved in the budget law but was not paid for years due to various reasons (including a change of ministers and governments, and the implementation of concurrent competitor programs).	Participant 02
		Insufficient financial resources were the main barrier to implement UFPP.	Participant 07
		The financing of the UFPP by insurance, Tax, and public resources required rules and guidelines.	Participant 04
	Insurance issues	The insurance provided good support at the beginning of the FPP. Their support was because they approached their main tasks (strategic purchasing, resource management, cost saving, promoting quality, efficiency, equity, and responsiveness in health service provision). Over time, due to budget deficits, insurance support decreased and insurance problems increased.	Participant 02
		In the context that currently exists and the unusual and ineffective contracts that insurance organizations currently have with doctors, they cannot control costs.	Participant 02
		The diversity of insurance organizations and multiple insurance funds and lack of pooling was a barrier to financing UFPP properly.	Participant 01
		Weak interaction between the health system and insurance organizations at the beginning of the program implementation was another factor in the failure of the program.	Participant 02
Payment	Wrong payment mechanism	The payment system in UFPP was a fee for services (FFS). A method in which physicians are paid for each service performed. While the proper payment system in UFPP was per capita payment in the Iran context. To implement the per capita policy as a preferred payment mechanism, physicians had to cover a certain number of patients and were paid according to the number of services provided. However, the per capita scheme did not fully take into account the services actually provided.	Participant 01
		The most common model of payment to specialists is through FFS.	Participant 07
	Inappropriate payment	The salaries of the specialists were sometimes inadequate.	Participant 01
		A large number of specialists in Fars province, who were generally in the special clinic, despite the fact that the university was interested in their payment correctly and through the referrals system, created disruptions in the proper implementation of the plan.	Participant 01
		Compared with other jobs, the salaries of staff providing family physician services are low, and this also has a negative impact on motivation to attend the program.	Participant 06
		Delay in payment to physicians was an important factor in the failure of the program.	Participant 05 Participant 06
		Failure to pay on time and irregularity in payments was an important factor in the failure of the program.	Participant 08
		Delay in payments by insurance organizations was an important factor in the failure of the program.	Participant 07

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Payment	Inappropriate payment	The common share of caregivers from FP's capitation led to some issues including out-of-pocket payment to caregivers due to delays in receiving capitation and discrimination in paying caregivers due to physicians' preferences.	Participant 06
Regulation	Centralized planning	The decision-making process was top-down and centralized rather than collaborative and participatory, thus leading to debates and controversies.	Participant 01
		Lack of necessary delegation in UFPP implementation was one of the barriers to the fully effective implementation of UFPP.	Participant 01 Participant 08
	Unclear laws	The related rules and guidelines were not very clear.	Participant 02
Behavior	Cultural problems	The culture of many people's lack of trust in the services provided by GPs and the willingness to use the services of specialists was one of the barriers to the fully effective implementation of UFPP.	Participant 02
		Lack of trust in health care at low levels of service delivery was one of the barriers to the fully effective implementation of UFPP.	Participant 06
		The unfamiliarity of the public with the correct use of FP services and visiting their FP only to be allowed to visit a specialist without any cost was a problem to the effective implementation of UFPP.	Participant 01
		Little attention was paid to the required perquisites such as cultural infrastructure growth.	Participant 02 Participant 05 Participant 06
		The egoistic manner of medical specialists was a problem to the effective implementation of UFPP.	Participant 01 Participant 06
	Determination	At the beginning of the implementation of UFPP, the determination of the university was high, but there were challenges with the Association of General Practitioners, insurance organizations, parliamentarians and officials, and local and native politics.	Participant 02
		At the end of the 10th government, with the change of the minister, there was a change in the national determination.	Participant 02
		The 10th, 11th, and 12th government ministers were not in favor of the UFPP and wanted to stop the program.	Participant 02 Participant 04
		The UFPP gradually lost its national and regional determination.	Participant 01
	Conflict of interest	Lack of a well-designed and efficient referral system. For this reason, horizontal referral happened especially in the private sector (the physician referred to his private clinic). As a result, the physician would create induce demand or refer the patient to himself.	Participant 02 Participant 05
		Some medical specialists think that the UFPP may reduce their patient numbers and consequently their income.	Participant 04
		Due to the conflict of interests, the tariffs are not communicated correctly.	Participant 04
		The conflict of interests of the some university chancellors caused a disruption in the project implementation process. The extent that specialist doctors were rewarded with two visits in addition to their own visit and a high share of the income of the faculty members was provided from there. Therefore, the cost of outpatient services in Fars province increased a lot.	Participant 01

* UFPP: Urban Family Physician Program.

Financing

The UFPP faces several financial challenges, including insufficient government budgets. This challenge has been mentioned in the study by Mehrolhassani et al. (2021) that, despite the legal approval of the budget of the UFPP, due to various reasons such as the change of administrators and economic conditions, there are usually fluctuations in the payment of the budget [54]. Besides this, the existence of different insurance funds with different policies and approaches is a challenge for Iran's health system, which has also faced difficulties in financing the UFPP [41, 44, 54]. In fact, the existence of multiple health insurance funds has caused insurance mechanisms such as resource pooling, risk distribution, and cross-subsidizing to not be carried out well. Although, according to the law of the fifth development plan, health insurance funds should have been merged and integrated, this policy has not yet been implemented. This finding has been mentioned in the study by Dehnavieh et al. (2015), which found that the existence of multiple health insurance funds and the absence of a single insurance system is one of the major challenges of implementing the UFPP in Iran [39]. Therefore, in addition to providing stable financial resources for the UFPP, which is of course very difficult considering Iran's economic conditions, fundamental reforms should be carried out in Iran's health insurance sector in order to make it more effective.

Tab. V. Solutions to improve the implementation of urban family physician program in Iran (qualitative study).

Five control knobs	Categories	Codes	Participant ID
Organization	United Stewardship	The stewardship of the health system should be strengthened and centralized in Health Ministry	Participant 01
	Involving political actors	The correct implementation of the program in the whole country requires national determination and political determination.	Participant 02 Participant 04
	Gradual implementation	The UFFP should be implemented step by step and according to the schedule.	Participant 01 Participant 02
		First, solve the problems of the two pilot provinces that have been identified during the last ten years and bring them to standard status, and gradually implement the plan in the rest of the country's provinces with a specific schedule and step-by-step.	Participant 02
	Considering the successful models in other countries	Follow the successful countries in implementing the UFPP as an example.	Participant 01
	Enhancing intra- and inter-sectoral collaboration	The sequence of actions of the UFFP should have a logical timing. Also, promoting inter-sectoral collaboration as the stakeholders of family physician policy is necessary.	Participant 02
		The UFPP is not specific to the MoHME, but it is a mega project and should have comprehensive collaborations.	Participant 06
		The national planning meetings should be held in the presence of the president and ministers related to the program.	Participant 04
	Improving referral pathways	We could apply referral limits, and assign franchises to hinder the excessive referrals to FPs. Zero franchises can be devoted only to lower-income percentiles while for rich regions a franchise can be assigned as mandatory. The people who go to FPs more than a specific amount will have to pay a franchise.	Participant 01
		Implementing the UFPP with the compulsory referral system.	Participant 04 Participant 05
		Implementing the UFPP with the compulsory referral system.	Participant 05
		Implementing the UFPP with the gatekeeper role and the compulsory referral system should first be culturally institutionalized in the officials, MPs, ministers, and members of the government, then it should be imposed on the people.	Participant 02
		With the correct implementation of the UFPP and the compulsory referral system, the FP gains credibility in society and gains the trust of the people.	Participant 01 Participant 02
		Develop the primary health care (PHC) of the country actively through caregivers and FPs and under the supervision of the UFPP.	Participant 02
		As regards, the family physician plan being aimed at confronting people with the first level of services, the model of providing outpatient and specialized and sub-specialized services must be changed.	Participant 01
		The UFPP services should be regionalized. It is better that the regionalization is stratified into four levels (macro level, community level, family level, and basic level).	Participant 06
	Establishing electronic health records	The development of electronic health records at all three levels is one of the important infrastructures in the implementation of UFPP.	Participant 01 Participant 05 Participant 08
	Using shift rotation	Rotate the shifts of family physicians so they can leave at any time, without worrying about a replacement physician.	Participant 01
		Adjusting the working hours of family physicians from 8 to 14 and from 14 to 21 and assigning several patients to two FPs during these hours in order to prevent FP's dual practice and to focus more on the family physician program.	Participant 07
	Establishing an effective service packages	UFP service packages should be developed based on the burden of the disease.	Participant 01 Participant 02

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Organization	Nationwide implementation	The UFPP should be implemented nationwide.	Participant 04
	Moving towards prevention	The health status of the population covered should be actively followed up, by FPs and caregivers and we should move from a treatment-oriented mode to prevention.	Participant 05
	Accountability	Promote accountability in the FP to improve the implementation of UFPP.	Participant 05
	Effective monitoring and evaluation	Creating a powerful monitoring and evaluation system based on the payment system to provide high-quality services by physicians and the relevant proper evaluation criteria should be set for service receivers.	Participant 01
		Use accreditation method for evaluation the UFPP.	Participant 01
		The evaluations should change from quantitative to qualitative and compare the performance of each FP with the total performance of the province and the country.	Participant 05
		The deputy health department should continuously monitor the indicators and health status of covered people.	Participant 05
Behavior	Promoting the culture of users and providers	Social marketing is needed so that people accept UFPP services. The mass media and opinion leaders should promote its acceptance. Using UFPP services should be represented as a value.	Participant 01
		Increase the covered population awareness by enhancing the culture of FP's correct use.	Participant 01
		The behavior change must occur in both service recipients and providers. This change is gradually obtained in the community and requires trust building.	Participant 02
	Enhancing incentive mechanisms	Improve incentive mechanisms for specialist collaboration.	Participant 03
	Voluntary participation	The FP should be voluntary for the GPs, that is, if the physicians like to participate in the program and use its benefits and if they do not want to leave the program and give the covered population to another physician.	Participant 09
	Establishing a comprehensive education	Improving the ability of GP and training the fundamental differences between FP and GP, behavior to the patient as an FP, and having a holistic view of diagnostic-curative topics as specific courses for FP. A short mandatory course at the beginning of the FP contract, with a continuous professional development program, should be arranged.	Participant 01 Participant 03 Participant 06
		Reforms in medical curriculum are recommended	Participant 02
		Improving the ability of caregivers by arranging continuous professional development programs.	Participant 01 Participant 03 Participant 08
		Necessary training should be given to the covered population in order to appeal to people's trust and encourage their active collaboration in this program.	Participant 05
Financing	Moving towards effective insursnce	The working model of the insurance fund must be changed and the financial resources must be integrated virtually till the time their real polling can be reached.	Participant 01
	Considering stable resources	Providing sustainable financial resources for the continuous implementation of UFPP is necessary.	Participant 01 Participant 04 Participant 05
		Participation of FP and specialists in the financial risks imposed on the health system and payment system reform.	Participant 01
	Splitting between users and providers	We must make the per capita realistic and eliminate the financial and monetary relationship between the patient and the FP.	Participant 05
Payment	Moving towards mixed payment mechanisms	Establish a performance-based payment system up to the service package ceiling.	Participant 01 Participant 05
		Establishing health care services for all urban dwellers with a per capita payment system.	Participant 01

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Payment	Moving towards mixed payment mechanisms	A combination of payment methods is more appropriate to increase the efficiency and effectiveness of the payment system and improve the expected results and the method of payment per capita is generally used alongside other methods.	Participant 01
	Splitting between purchaser and provider	Establishment of appropriate rules for payments to solve financial problems. It's better for the Ministry of Welfare to be assigned the infrastructure and payments for the FPP instead of the Ministry of Health, for the MoHME to strengthen its surveillance role.	Participant 06
		Provider–purchaser separation can lead to success and reduce conflicts of interest in Iran's health system.	Participant 01
		One of the most important solutions is maintaining order in payments and timely payment to FPs.	Participant 07 Participant 08
Regulation	Setting rational tariffs	Setting medical tariffs rationally and based on the relative value of health services is needed infrastructures, which are deemed necessary for the effective implementation of UFPP.	Participant 01 Participant 03
	Strengthening clinical guidelines	Practice the referral system, regularization, and strategic purchase of services based on the compilation of clinical guidelines and through the UFPP.	Participant 01 Participant 08
	Clarifying the legal requirements and authorities	Clarifying the legal requirements of planning to provide resources and facilitate the UFPP implementation plan.	Participant 01
		Special powers should be obtained for the national headquarters of the UFPP, so that during the implementation of the program, there is no need to obtain a license, approve the law, and delegate powers through the parliament.	Participant 04
		The necessity of developing a referral system and family physician program in all cities across the country is the most important dimension of Iran's upstream health policies.	Participant 07
	Decentralization	Delegating provincial powers to facilitate the implementation of the UFPP.	Participant 01 Participant 08

Payment

Inappropriate payment mechanisms, both in our study and in other published studies, have been raised as one of the most important obstacles to the effective implementation of the UFPP in Iran. In this regard, relevant evidence showed that payment mechanisms such as per capita payments do not motivate UFPP's employees well [35, 39, 57]. According to the study by Doshmangir et al. (2018), although bonuses are also paid in order to improve the quality of services provided to employees, they still cannot compensate for the services provided [41]. That is why in many countries they use mixed payment methods, including monthly salary, bonus, capitation, and fee-for-service (FFS) [41]. Using a mix of payment methods can help motivate providers, stop unnecessary visits, and improve the quality of care services, among other things [76]. Further, the delay in payments is a common challenge in this dimension, which has significantly caused the dissatisfaction of the employees of this program [44, 45]. In line with this finding, Arab et al. (2014) reported that delayed payments was one of the main reasons for family physicians' dissatisfaction [77]. Therefore, with timely payments, we can move in the direction of improving the level of motivation and satisfaction of employees.

Regulation

Based on our findings, the rules are cumbersome, and since there is no rigorous monitoring and evaluation process, the supervision has become very complicated. Other studies [39, 45] have also expressed such a finding and believe that the lack of clarity in the laws and regulatory approach has caused the implementation of the family physician program to face a serious challenge. Furthermore, centralized planning is another challenge related to the legislation of the family physician program, which, of course, is a feature of the entire Iranian health system and is not specific to this program [78]. In fact, there is a need for the role of provincial governments to become more prominent in the planning process of such community-oriented programs. So, one of the policies that needs to happen before the UFPP can be pushed forward in the coming years is for local governments to be more involved and given real power, so that they can make decisions faster and spot problems more quickly.

One of the notable findings was that, despite some legal requirements, changing in governments and administrators are accompanied by changes in attention to programs such as family physician. Meanwhile, such reforms require medium- and long-term planning in order to achieve their desired impacts. In agreement with this finding, evidence has shown that, as with other

reform programs in Iran, changes in governments and senior managers significantly affect the implementation of previous programs [45, 54, 74]. In fact, personal and group preferences cause the implementation of a legal program to be challenged. Therefore, it is necessary to create a clear road map for the health system reforms and to make the managers adhere to the plans so that even with the change of managers, the implementation of the plans will not be disturbed.

Behavior

Cultural issues on the part of both service recipients and providers have made the provision of UFPP services problematic [39, 40, 45, 59]. Based on the findings, some people do not have a proper view of the knowledge and performance of general practitioners in the family physician program. Therefore, a significant proportion of patients prefer to be evaluated by a specialist in the first place. Indeed, these conditions are caused by the lack of sufficient knowledge of the service recipients about the services of the UFPP and the referral system [44, 66]. According to a study done by Janati et al. in 2010, more than half of the people who went to the emergency room for non-urgent problems could have been treated by a general practitioner [79]. Furthermore, the findings showed that some specialists have an egoistic manner and are not very willing to cooperate with the family physician program. In fact, they think that the implementation of such a program can reduce the number of patients and therefore FPs' income [39, 44]. Moreover, lack of private sector participation in UFPP has made the private sector, as a significant beneficiary of Iran's health system, uninterested in cooperating with this program. These factors have led to a series of conflicts of interest that have significantly challenged the effective implementation of the UFPP. In response, effective strategies need to be implemented in order to raise the public's and health professionals' awareness about the UFPP and its main functions. Nonetheless, it should also be noted that improving culture and behavioral changes is very complex, time-consuming, and requires national commitment and community-oriented educational programs.

Conclusion

This study showed that despite the passing of a decade of the UFPP, there are still serious challenges related to all five dimensions: organization, financing, payment mechanisms, regulation, and the behavior of providers and recipients. Therefore, the promotion of this program requires solving the existing implementation challenges in order to achieve the predetermined goals. The ideas in this study can be used to improve the current program in Fars Province and bring it to other regions of Iran.

Ethics approval and consent to participate

The ethical committee of the Shiraz University of Medical Sciences approved the study previously (IR. SUMS.REC.1401.514). Participants were aware of their voluntary participation and that they could leave the study freely at any stage. A signed informed consent form was also received from participants prior to each interview. All methods were performed in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest statement

The authors declare that they have no competing interests.

Authors' contributions

KBL, BH, SRN, SS: conceptualization. MH, FZ, SRN, SS, MF, MM: data collection. KBL, MG, FZ, SS, MF, FR: data analysis. KBL, BH, SS, MH, FZ, MF: writing and initial draft. KBL, BH, SS, MH, FZ, MF, FR, SRN: writing, review and editing. MM: editing.

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Supplementary file 1: Qualitative findings

Organizational Challenges

Integrated stewardship of the health system is one of the important factors in carrying out the UFPP. But fragmentation and multiple entities in the stewardship role of the MOHME were obstacles to implementing UFPP in Iran.

"The fragmented stewardship of the MOHME and weak governance in Iran's health system, coupled with instability in policies, led to failure in the implementation of the UFPP in Iran."[Participant 02]

In addition, the long working hours of the UFPP due to single work shifts and inadequate family physicians that led to a long waiting list had increased the public's and physicians' dissatisfaction.

"The working hours of FPs were from morning until evening, due to the high volume of visits and high level of responsibility. Also, bureaucracy has dramatically increased the workload."[Participant 02]

The proper educational programs for providers are an important part of the establishment of the UFPP. It seems that one of the reasons for the failure of UFPP in Iran was the educational problems and lack of development of the necessary skills to be a FP. Also, FPs lack innovation in improving healthcare, and their education is focused solely on treatment.

"The lack of a community-based vision in the educational system, inadequate training for service providers, and physicians' lack of readiness and necessary skills for caregiving as an FP all posed challenges to the UFPP's full implementation."[Participant 01]

An incomplete referral system was a severe obstacle for the UFPP. Without an efficient referral system, the most important functions of FPs as gatekeepers for access to specialized care have not been properly practiced.

"The absence of a well-designed and efficient referral system had resulted in numerous issues, including horizontal referral, particularly in the private sector, induce demand, and physician self-referral."[Participant 05]

The weakness in health monitoring and evaluation by the MOHME, the medical universities, and insurance companies, the inadequacy of continuity of supervision on the performance of the services, the absence of a native evaluation program, and a lessened emphasis on outcome indicators had led to the inefficiency of the UFPP in Iran.

"There is a poor monitoring and evaluation system in the health system of Iran to assess the performance of the UFPP service providers."[Participant 01]

Poor incentive mechanisms such as inadequate remuneration, unreasonable facilities at residence, a poor working environment, political interference, inadequate supplies, and medical facilities all contributed to a lack of motivation in FPs.

"Unsuitable salary requirements, a lack of job security, and a lack of opportunity for continuing education were the most common reasons for FPs to leave the program."[Participant 07]

UFPP needs an efficient electronic health information system (HIS) to provide physicians with patients' information centrally and provide program managers with more comprehensive information, such as the medication and equipment used and the type of services provided to the client. The HIS must provide communication at different levels. A lack of strong information technology infrastructure was another serious obstacle to the UFPP.

"The lack of an electronic health database of individuals and suitable infrastructure for the development of the HIS was an obstacle to UFPP implementation that needed to be resolved at the highest levels of the healthcare system."[Participant 08]

Participants talked about the administrative problems and hurdles that family physician programs in Iran's cities face.

"At the beginning of the implementation of the UFPP, service packages were not defined. Also, the service package was not defined to include follow-up on the patient's health by the FPs. So there was a gap between the UFPP plan and its implementation."[Participant 06]

"The coordination meetings of the National Family Physician staff and its executive staff have not been held due to inadequate management and political commitment. So, there was no political interest in the process of implementing the UFPP."[Participant 03]

There is a need for collaboration between family physicians and the organizations that provide healthcare services to efficiently implement UFPP. However, the lack of inter-sector collaboration and public participation hampered the full implementation of UFPP in Iran.

"The lack of coordination between the ministries of health and welfare has caused confusion and problems for both providers and recipients of services, as well as for the insurance system."[Participant 02]

Financing challenges

The participants believed that the implementation of the UFPP was affected by two main factors: budget deficits and insurance problems. According to experts, the non-realization of sustainable financial resources for the continuous implementation of the UFPP, while adequate funds were available to launch the plan at the beginning, was the key reason for the failure of the plan. Fragmentation in health insurance system funds and the health system's interaction with insurance organizations challenged urban FP program performance even further. In this regard, one of the participants mentioned:

"Insurance provided good support at the beginning of UFPP. Their support was because they approached their core mandates (strategic purchasing, resource management, cost savings, promoting quality, efficiency, equity, and responsiveness in health service provision). Over time, due to the budget deficit and fragmented insurance funds, insurance support decreased and insurance problems increased."[Participant 02]

PAYMENT CHALLENGES

The payment system has an important role in providing appropriate health services. Many participants believed that the unfavorable payment mechanism in the UFPP and the inappropriate payment of salaries of health workers in the UFFP, as well as the lack of clarity and notable income gap among the members of a health team, had led to delays in refunding the payments to the FPs and increased their dissatisfaction with the UFPP. In this regard, one of the participants mentioned:

"Physicians had to cover a certain number of patients and were paid based on the amount of services provided in order to implement the "per capita" payment mechanism as the preferred payment mechanism. The per capita mechanism did not fully take into account the services actually provided. Also, delays in the payment of salaries have caused many physicians not to continue their cooperation."[Participant 01]

REGULATION CHALLENGES

More authority in UFPP has not been delegated, which could lead to motivation in the management of people's health and play an important role as a gatekeeper.

"The decision-making process was top-down and centralized rather than collaborative and participatory, thus leading to debates and controversies due to the lack of necessary delegation in UFPP implementation."[Participant 01]

BEHAVIOR CHALLENGES

Many participants believed that the cultural problems of service receivers and service providers and the poor information process were the obstacles to establishing this plan because the necessary infrastructures were not ready to implement the project. In this regard, one of the participants mentioned:

"At the beginning of the plan, little attention was paid to the required prerequisites, such as cultural infrastructure growth. The unfamiliarity of the public with the correct use of FP services led to people visiting the FP only to be allowed to visit a specialist without any cost."[Participant 06]

Another behavioral challenge and obstacle to implementing this program was the lack of national and political determination in the years of plan implementation.

"At the beginning of the implementation of UFPP, the determination of the universities was high, but at the end of the 10th government, with the change of the minister, there was a change in the national determination. Also, the 11th and 12th government ministers were not in favor of the UFPP and wanted to stop the program." [Participant 02]

The establishment of the FPP in urban regions faces some challenges, such as a powerful private sector with high conflicting interests among family physicians and between specialist physicians and GPs.

"Because family physicians and specialists make very different amounts of money, putting in place the family doctor program with the gatekeeper role and the mandatory referral system will make it more likely that there will be a conflict of interest, which will make the problems worse."[Participant 04]

SOLUTIONS

Organizational-related solutions

According to the suggestions of the participants, strengthening and centralizing the stewardship of the health system is one of the important factors for the implementation of the UFPP in Iran. It is more effective to implement this plan in the entire country step by step and according to the schedule and logical timing. The UFPP must be implemented with the compulsory electronic referral system. It's important to promote inter-sectoral collaboration between service presentation levels and beneficiary organizations. UFP service packages should be developed based on the burden of the disease. It's better to use a consultation form instead of a referral form because specialists pay more attention to the views of GPs. To prevent excessive referrals to FPs, we could impose referral caps and limit zero franchises to lower-income percentiles. To decrease the workload of FPs, we could design rotational shifts. It needs to create a powerful monitoring and evaluation system based on the payment system to allow FPs to provide high-quality services. These suggestions will be realized if there is a political and national determination to implement the plan.

"My suggestions to improve UFPP implementation in Iran are; strengthening the stewardship of the MoHME, Implementing the program step by step, using a consultation form, compulsory referral system, enhancing the people's culture through education, limiting Zero franchises and excessive referrals to FPs by rules, Rotating the shifts of FPs, designing UFP service packages based on the burden of the disease, strengthening the cooperation of the private sector, improving the model of providing outpatient and specialized and sub-specialized services

according to successful countries in implementing the UFP, improving monitoring and evaluation system based on the payment system, and using the accreditation method for evaluating the UFPP."[Participant 01]

FINANCING-RELATED SOLUTIONS

The UFPP in Iran compensates services on the basis of a per capita payment system based on coverage of a defined population. According to the opinion of the participants, Iran's health system should be creating and strengthening sustainable financing strategies to develop equity in healthcare financing through a progressive financing policy. Participants suggest designing a financial system based on the capabilities of the public and private sectors for an entire population in a region and based on a defined per capita cost supervised by the provincial health care and treatment network.

"We must make the per capita realistic and eliminate the financial and monetary relationship between the patient and the FP. Also, we must be able to make changes according to the conditions of each province so that we can respond to all the needs of the covered population."[Participant 05]

PAYMENT-RELATED SOLUTIONS

The payment system for the UFPP in Iran was not appropriate. Several interviewees highlighted the importance of designing a payment system based on mixed payment methods, including a combination of capitation, FFS, and bonuses.

"A combination of payment methods is more appropriate to increase the efficiency and effectiveness of the payment system and improve the expected results, and the method of payment per capita is generally used alongside other methods."[Participant 01]

"We should establish a performance-based payment system up to the UFPP service package ceiling and maintain order in payments to FPs."[Participant 05]

REGULATION-RELATED SOLUTIONS

According to the opinion of the participants, the required infrastructures for planning and launching UFPP included: setting medical tariffs rationally, establishing the referral system, strategic purchasing of services based on the compilation of clinical guidelines, developing electronic health records at all three levels, clarifying the legal requirements of the plan, regionalizing the UFPP services, and delegating provincial powers.

"Setting medical tariffs rationally and based on the relative value of health services, strategic purchasing of services based on the compilation of clinical guidelines, developing electronic health records at all three levels, Clarifying the legal requirements to provide resources, and delegating provincial powers are suggested to facilitate the implementation of the UFPP."[Participant 01]

BEHAVIOR-RELATED SOLUTIONS

The implementation of the family physician program needs culture-building among people and service providers. In this regard, interviewees suggest orienting the public's mentality toward the program. The mass media should advertise the program and be involved with the program. Also, urban community-based medical education for GPs should be developed.

"Social marketing is needed so that people accept UFPP services. The mass media and opinion leaders should promote its acceptance. Using UFPP services should be represented as a value."[Participant 01]

"Social marketing is needed so that people accept UFPP services. The mass media and opinion leaders should promote its acceptance. Using UFPP services should be represented as a value."[Participant 02]

ERRATA CORRIGE

Pubblichiamo di seguito 7 Abstract che per un disguido non sono stati inseriti negli Atti del 55° Congresso Nazionale SItI (Padova, 28 settembre - 1 ottobre, 2022) - J Prev Med Hyg 2022; 63 (Suppl. 1): E1-E443.

COMUNICAZIONI ORALI

INFEZIONI CORRELATE ALL'ASSISTENZA E ALL'ANTIBIOTICO-RESISTENZA

Abstract Code: SIT16577-06

Caratterizzazione epidemiologica e molecolare di *Acinetobacter baumannii* durante la pandemia COVID-19

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INTRODUZIONE

La pandemia COVID-19 ha posto richieste straordinarie al sistema sanitario, con conseguenti modifiche nelle pratiche di routine di assistenza dei pazienti con un impatto sulle infezioni correlate all'assistenza (ICA) e l'antimicrobico-resistenza. Le infezioni da *Acinetobacter baumannii* rappresentano un importante problema associato all'assistenza sanitaria e diversi studi hanno riportato coinfezioni in pazienti COVID-19. L'obiettivo del presente studio è stato quello di caratterizzare gli isolati di *A. baumannii* da pazienti COVID-19 inclusi nello studio EPIRADIOCLINF condotto presso l'Azienda Ospedaliero Universitaria Policlinico "G. Rodolico - San Marco" di Catania.

MATERIALI E METODI

Gli isolati sono stati raccolti prospetticamente da pazienti COVID-19 ricoverati in tre reparti (UOC Malattie infettive e tropicali, MCAU e Terapia Intensiva) della struttura sanitaria in studio. Per analizzare le relazioni clonali gli isolati sono stati sottoposti a tipizzazione molecolare mediante analisi di macrorestrizione del DNA genomico dopo *Pulsed Field Gel Electrophoresis* (PFGE) utilizzando il sistema CHEF-DRIII.

RISULTATI

Complessivamente, sono stati analizzati 64 isolati di *A. baumannii* provenienti da 48 pazienti affetti da COVID-19. L'analisi PFGE ha identificato 8 pulsotipi PFGE non correlati (denominati da A a H). È interessante notare che l'analisi della clonalità ha indentificato un episodio di trasmissione clonale, sostenuto dal pulsotipo B che presentava 3 sottotipi (denominati B1-B3). Il clone B è stato identificato in 55 dei 64 isolati (86%) provenienti da 41 dei 48 pazienti (85,4%). I restanti pulsotipi PFGE erano *pattern* singoli associati a ceppi sporadici. Per quanto riguarda i profili di resistenza, 59 isolati di *A. baumannii* erano resistenti ai carbapenemi (concentra-

zione minima inibente [MIC] per meropenem > 8; imipenem MIC > 8), alla gentamicina (MIC > 4), alla ciprofloxacina (MIC > 1) e alla tobramicina (MIC > 4); 56 isolati erano resistenti al trimetoprim e sulfametossazolo (MIC > 4/76) e 53 all'amikacina (MIC > 16).

CONCLUSIONI

Le infezioni causate da *A. baumannii* multiresistente rappresentano una minaccia ed un importante problema di Sanità Pubblica. La nostra analisi conferma alti livelli di trasmissione clonale di *A. baumannii* in pazienti COVID-19 e suggerisce l'implementazione di strategie efficaci di prevenzione e contenimento delle ICA in tutti i reparti ospedalieri..

Abstract Code: SIT16153-96

Cost-effectiveness analysis of antimicrobial prophylaxis strategies to prevent blood stream infections among onco-haematological transplant recipients

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BACKGROUND

Bloodstream infections (BSIs), in particular due to extended-spectrum beta-lactamase and carbapenemase-producing Enterobacteriaceae (ESBL, KPC), are life-threatening complications for patients with haematological malignancies (HM) receiving transplantation. Antibiotic prophylaxis with fluoroquinolones (FQP) has been correlated with increased resistance rates among HM patients, however the role of FQP remains a debated issue. The objective of this study was to evaluate costs and effects associated with two alternative strategies: FQP vs. no prophylaxis.

METHODS

A decision-tree model was built integrating retrospectively collected data from a single transplant center, part of a tertiary teaching hospital in Northern Italy. Probabilities, costs (in terms of costs associated with length of stay, LOS), and effects (in terms of life-years gained, LYs) were considered in the assessment of the two alternative strategies. Probabilities of colonization (positive rectal swab), BSIs, ESBL/KPC BSIs and mortality associated with infection, as well as median duration of length of stay were calculated based on data collected between 2013 and 2021. The center applied the strategy of FQP between 2013 and 2016, and of no prophylaxis between 2016 and 2021. The cost of a single bed-day was obtained from hospital management.

RESULTS

Data on 326 patients were collected during the considered time period. Overall, the rates of colonization, BSI, KPC/ESBL BSI, and mortality were 19.06 (95%CI 15.14-23.49), 42.27 (37.12-47.54), 8.84 (6.13-12.25), 20.72 (16.67-25.26) respectively. The median LOS was 32 (IQR 29-37.75), 35 (30-44), and 35.5 days (32-43) for patients with no infection, BSI, and KPC/ESBL BSI respectively. A mean bed-day cost of 132€ was estimated. Based on estimates from the literature, a 20.8% reduction on Italian life expectancy was applied to estimate the life expectancy for patients receiving allogeneic blood or marrow transplantation. The median age at admission was 53 years, therefore 8.42 LYs gained for patients surviving were considered (applying a 3% discounting rate). According to the cost-effectiveness analysis, FQP was the dominating strategy. However, incremental costs associated with no prophylaxis of under 20€ per patient were estimated, with a decremental effect of 0.05 LYs gained (18.25 days).

CONCLUSIONS

Given the small differences in terms of costs and effects between the two strategies, no prophylaxis seems an appropriate choice. Furthermore, this analysis did not consider the broader effect on hospital ecology of multiple doses of FQP, which could provide further support for the strategy of no prophylaxis.

Infezioni Correlate all'Assistenza: l'importanza della sorveglianza ambientale in un *outbreak* da *Candida parapsilosis*

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INTRODUZIONE

Le Infezioni Correlate all'Assistenza (ICA) rappresentano la complicanza più frequente tra i pazienti ospedalizzati. Sebbene prevalentemente determinate da batteri, nel corso degli ultimi anni sempre più spesso sono state documentate infezioni micotiche sostenute per lo più dal genere *Candida*. In particolare, *Candida parapsilosis,* un lievito commensale della cute dell'uomo, è frequentemente responsabile di sepsi catetere-correlate. Studi recenti hanno riportato *outbreak* nosocomiali dovuti anche a ceppi resistente agli azoli.

Nel periodo aprile-maggio 2022, in 10 pazienti ricoverati in Terapia Intensiva è stata diagnosticata una sepsi da *C. parapsilosis* fluconazolo-resistente. Al fine di individuare la possibile sorgente di infezione e controllarne la diffusione, è stata condotta una indagine sia nell'ambiente sia sul personale di assistenza.

MATERIALI E METODI

L'indagine è stata eseguita nei box di degenza, nelle postazioni reception e sulle mani del personale di assistenza. Mediante l'uso di tamponi sterili, sono state esaminate 74 superfici *high-touch* (spondina letto, monitor ventilazione assistita, pompe di infusione, computer postazioni di lavoro) e le mani di 47 operatori. I tamponi sono stati insemenzati su piastre di Sabouraud, gli isolati identificati mediante MALDI-TOF

RISULTATI

Complessivamente, il 9,5% delle superfici è risultato positivo per *C. parapsilosis*: 3 monitor touch-screen per la ventilazione assistita, 2 pompe di infusione a siringa nei box di degenza, 2 tastiere computer presenti nelle postazioni reception. Le mani degli operatori sono risultate sempre negative.

CONCLUSIONI

Nonostante l'impiego di procedure e protocolli di prevenzione, le ICA costituiscono ancora un rilevante problema di Sanità Pubblica. L'emergenza di stipiti di *C. parapsilosis* fluconazolo-resistente richiama l'attenzione sui miceti come possibili responsabili non solo di *outbreak* nosocomiali ma anche di nuovi aspetti relativi all'AMR . Sugli stipiti isolati sono in corso indagini molecolari che permetteranno di dimostrare l'eventuale correlazione genetica tra ceppi clinici e ambientali. Sebbene *C. parapsilosis* non sia mai stata isolata dalle mani degli operatori, dimostrando una corretta adesione alle procedure di igiene delle mani, la presenza di questo lievito sulle superfici *high-touch* è indicativa di un utilizzo non corretto dei dispositivi di protezione individuale. Infatti, guanti non sostituiti dopo le manovre assistenziali, favoriscono la circolazione di ceppi nell'ambiente e la trasmissione ad altri pazienti.

I nostri dati suggeriscono l'importanza di pianificare, oltre a programmi di disinfezione ambientale, adeguati corsi di formazione rivolti a tutto il personale di assistenza, per prevenire e ridurre significativamente il rischio di ICA.

La sorveglianza delle infezioni da *Clostridium difficile* in ambiente ospedaliero: ruolo dell'epidemiologia molecolare e dell'audit interno come strumenti per il contenimento delle ICA

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INTRODUZIONE

L'infezione da *Clostridium difficile* (CD) in setting ospedaliero richiede, ad integrazione delle procedure di contenimento delle infezioni correlate all'assistenza (ICA), una rapida e ragionata riorganizzazione dei posti letto finalizzata all'attuazione dell'isolamento da contatto. Scopo del presente studio è documentare il ruolo degli audit nel monitoraggio epidemiologico e come le indagini di biologia molecolare possano rivelarsi elementi utili nella definizione di cluster di infezione.

MATERIALI E METODI

In un reparto di degenza di 10 posti letto della AOUP "Paolo Giaccone" di Palermo, nel periodo 19-27 Maggio 2022, sono occorsi 6 casi di infezione da CD tossigenico, identificati attraverso test immunocromatografico su campione di feci per ricerca dell'enzima *Glutamate dehydrogenase* e delle tossine A e B. Veniva pertanto avviato un audit al fine di identificare l'eventuale cluster infettivo e le possibili criticità occorse nel contenimento dell'infezione.

RISULTATI

Nel periodo in esame è stata osservata una prevalenza dei casi di infezione da CD pari al 66,7%, superiore rispetto ai 5 mesi precedenti in maniera statisticamente significativa (1,9%; p < 0,001). Le indagini di biologia molecolare attraverso test GenExpert® per *Clostridium* spp., hanno consentito di identificare 2 clusters in base al profilo tossigenico e al ribotipo (Cluster A: Tossina B+, Tossina Binaria+, 027-; Cluster B: Tossina B+, Tossina Binaria+; 027+). Valutati gli aspetti strutturali del reparto e gli spostamenti dei pazienti nelle camere di degenza, è stata ipotizzata, per il Cluster A, una diffusione attraverso contaminazione ambientale di una stanza di degenza. La ridistribuzione dei posti letto, insieme ad una incompleta applicazione delle procedure di sanificazione e di isolamento potrebbero aver rappresentato una verosimile concausa nella diffusione di CD nel periodo in esame.

CONCLUSIONI

Gli audit rappresentano un mezzo utile all'identificazione degli eventi avversi correlati all'assistenza ed uno strumento fondamentale nel miglioramento dei processi di cura. Le indagini di biologia molecolare possono essere funzionali al monitoraggio epidemiologico ed a supporto di scelte organizzative e gestionali nelle degenze ospedaliere. In ultimo, le prevedibili implicazioni legate al diffondersi delle ICA sottolineano la necessità di una stretta osservazione delle procedure di identificazione, gestione e contenimento dei microrganismi ad esse correlati. A seguito dell'audit in esame è stato avviato un programma di screening attraverso test imunocromatografico per ricerca di CD sui nuovi ricoverati, sono stati effettuati un intervento di formazione rivolto al personale ed una implementazione dei protocolli di pulizia e sanificazione del reparto in oggetto, i risultati dei quali saranno oggetto di valutazione.

Abstract Code: SIT16871-03

L'effetto di avvertenze e fattori situazionali sulla propensione all'autoprescrizione di antibiotici nella popolazione italiana: un'indagine sperimentale randomizzata

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BACKGROUND

L'inappropriata assunzione di antibiotici è uno dei fattori che determinano l'insorgenza di antimicrobico-resistenza ed è spesso associata all'autoprescrizione. Il presente studio si propone, nella popolazione italiana, di valutare l'effetto sulla propensione all'autoprescrizione di antibiotici di avvertenze comunemente usate in campagne di sensibilizzazione e fattori situazionali quali la quantità di antibiotici disponibili, l'accessibilità dei servizi sanitari, l'atteggiamento dei prescrittori verso l'antibioticoterapia.

METODI

Abbiamo arruolato mediante l'azienda Qualtrics un campione rappresentativo della popolazione maggiorenne italiana costituito da 1500 rispondenti, che hanno compilato, a inizio maggio 2020, un questionario online contenente due esperimenti decisionali randomizzati. Nel primo, i rispondenti sono stati randomizzati a non ricevere alcuna avvertenza o a ricevere un'avvertenza relativa rispettivamente agli effetti collaterali degli antibiotici, alla loro inefficacia su influenza e raffreddore, o all'impatto del loro uso scorretto sulle generazioni future. Nel secondo esperimento la randomizzazione è avvenuta per uno di otto scenari differenti tra loro per la combinazione di tre coppie di fattori: avere antibiotici per un giorno o sette; poter contattare il medico il giorno stesso o dopo tre giorni; ritenere che il medico prescriva antibiotici facilmente o meno. In entrambi è stata chiesta le probabilità da 0 a 100 d'iniziare un'antibioticoterapia autonomamente in caso di febbre. Sono state effettuate analisi di varianza a una via ($\alpha = 0,05$) per testare differenze significative nella propensione all'autoprescrizione tra le condizioni sperimentali, sull'intera popolazione e in sottopopolazioni selezionate.

RISULTATI

Complessivamente non si sono osservate differenze significative nella propensione all'autoprescrizione di antibiotici a seguito dell'esposizione alle avvertenze o ai fattori presentati. In chi afferma di non aver mai assunto antibiotici o non ricorda, l'avvertenza sull'inefficacia diminuisce di circa 10,5 punti percentuali la propensione all'autoprescrizione rispetto all'avvertenza sugli effetti sulle future generazioni (7,6 *vs* 18,1). La facilità di prescrizione determina un aumento della propensione all'autoprescrizione rispetto a chi la ritiene difficile nei soggetti senza figli (20,1 *vs* 16,6) e in chi non ha mai sentito parlare di antimicrobico-resistenza (20,9 *vs* 17,0). In chi ne ha sentito parlare, la disponibilità di farmaci per sette giorni aumenta l'autoprescrizione rispetto a chi ha disponibilità per un giorno (30,4 *vs* 24,1).

CONCLUSIONI

Lo studio mostra come, a livello aggregato, la propensione all'autoprescrizione di antibiotici sia difficilmente influenzabile mediante avvertenze o modifica di fattori situazionali. Tuttavia, una maggiore conoscenza dell'antimicrobico-resistenza potrebbe portare all'autoprescrizione solo in caso di disponibilità di un ciclo completo. Inoltre, la propensione del medico alla prescrizione di antibiotici sembra influenzare quella all'autoprescrizione in alcuni pazienti, evidenziandone la funzione educativa.

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Prevalenza delle ICA in un Policlinico Universitario prima e dopo la Pandemia (2019 *vs* 2021)

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INTRODUZIONE

Sono stati condotti 2 studi di prevalenza sulle infezioni correlate all'assistenza (ICA) presso l'Azienda Ospedaliero Universitaria Sant'Andrea di Roma (AOUSA) (450 posti letto), prima e dopo la pandemia (2019 *vs* 2020).

METODI

Gli studi di prevalenza, adottando il protocollo dell'ECDC,

hanno raccolto dati sulle caratteristiche demografiche e cliniche, le procedure invasive, l'impiego degli antibiotici, le infezioni ed i microrganismi responsabili.

RISULTATI

I 595 pazienti, rispettivamente 334 (2019) e 261 (2021), risultavano distribuiti tra reparti di chirurgia 49,2%, medicina 42,5% ed intensivi 8,2%, età media 66,0 ± 18,1 anni, mediana 69. Secondo il McCabe score, i pazienti con prognosi < 1 anni erano 13,6%, con prognosi 1 - 5 anni 24,4%, con prognosi > 5 anni 54,8%, i dati mancanti erano 7,2%. Il 34,8% dei pazienti sono stati sottoposti a chirurgia, 80,7% presentavano cateteri venosi periferici, il 38.1% catetere urinario, il 15,6%) catetere venoso centrale ed il 3,2% ventilazione meccanica.

In totale 89 (15,0%) pazienti su 595 avevano una qualche infezione (ospedaliera, da altro ospedale, comunitaria), 49 (14,7%) nel 2019 e 40 (15,3%) nel 2021. I pazienti con ICA sono stati 72 (12,1%), di cui 42 (12,6%) nel 2019 e 30 (11,5%) nel 2021. Altri 10 pazienti presentavano infezioni comunitarie (4 nel 2019 e 6 nel 2021), mentre 7 pazienti presentavano ICA da altro ospedale (3 nel 2019 e 4 nel 2021). I pazienti con ICA contratta presso l'AOUSA hanno sviluppato 78 episodi infettivi, 45 nel 2019 e 33 nel 2021, le più comuni erano infezioni delle vie respiratorie (47,5%), del tratto urinario (20,5%), setticemie (9,0%), del sito chirurgico (7,7%), da *C. difficile* (6.4%).

Il 59,7% dei pazienti avevano ricevuto almeno un antibiotico, con un decremento dal 62,6% nel 2019 al 55,9% nel 2021. Gli antibiotici sono stati prescritti prevalentemente per: profilassi chirurgica (27,9%), profilassi medica (18,9%), terapia per ICA (20,8%), terapia per ICA da altro ospedale (3,1%), terapia per infezione comunitaria (28,2%), altro (1,1%).

Nelle ICA acquisite presso AOUSA i Gram-negativi (61,7%) erano più frequenti dei Gram-positivi (31,6%). I principali patogeni responsabili delle ICA sono stati *Klebsiella* spp. (20,0%), *E. coli* (16,7%), MRSA (11,7%), *P. aeruginosa* (10,0%). Nell'indagine del 2021 non sono state riscontrate infezioni da *C. difficile*.

CONCLUSIONI

In generale la prevalenza delle ICA nel nostro ospedale risulta comparabile a quella di altri studi simili condotti in Italia ed in altri paesi. Inoltre, la riduzione della prevalenza nel 2021 potrebbe essere stata influenzata dal rafforzamento delle misure conseguenti alla pandemia.

Previous use of antibiotics and antibiotic-resistant *Acinetobacter baumannii* infection or colonization in ICU adult patients: a systematic review and meta-analysis

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BACKGROUND

Antibiotic resistance among bacteria in hospitals is a global health threat. Antibiotics use has generally been recognized as the main factor for the acquisition of antibiotic resistance, but this association still needs to be better defined for antibiotic-resistant *Acinetobacter baumannii*. The aim of this meta-analysis was to summarize the evidence between previous use of antibiotics and infection or colonization by antibiotic resistant *A. baumannii* in ICU adult patients.

METHODS

PubMed, Scopus, and Web of Science were searched from database inception to February 28th, 2022, for studies examining the association between previous use of antibiotics and antibiotic-resistant *A. baumannii* infection or colonization in ICU adult patients. Cohort and case-control studies, conducted in any country, that provided raw data, unadjusted, or adjusted odds ratio (OR) on the associations of interest were included. Quality of the studies was assessed with the Newcastle-Ottawa Scale. Inverse-variance random-effects meta-analyses was conducted according to the antibiotic class to produce pooled ORs and their associated confidence interval (CI), I^2 metric was used to quantify the heterogeneity. Stratification analyses by type of study (cohort studies vs case-control studies), type of control group (absence of *A. baumannii* infection or colonization vs antibiotic-sensitive infection), type of outcome (infection vs colonization vs colonization and infection by antibiotic resistant *A. baumanni*) and sample size (lower than the median vs higher/equal to the median of the studies sample sizes) were performed within each antibiotic class.

RESULTS

Overall, 24 studies of good quality were retrieved for systematic review and all but one were included in the meta-analysis. A significant association was found between antibiotic-resistant *A. baumannii* infection or colonization in ICU adult patients and previous use of aminoglycosides (OR = 2.35; 95% CI: 1.79-3.08), antipseudomonal penicillins (OR = 1.94; 95% CI: 1.31-2.86), carbapenems (OR = 3.58, 95% CI: 2.22-5.75), fluoroquinolones (OR = 1.59, 95% CI: 1.05-2.40), glycopeptides (OR = 2.24, 95% CI: 1.25-4.00), cephalosporins up to the third generation (OR = 1.27, 95% CI: 1.02-1.59) and nitroimidazoles (OR = 6.85, 95% CI: 2.31-20.39). Previous administration of aminoglycosides and carbapenems was significantly associated with infection or colonization by antibiotic-resistant *A. baumanni* in all stratified analyses such as type of study, type of control group, type of outcome and sample size.

CONCLUSIONS

This meta-analysis confirms the association between previous use of different antibiotics and infection or colonization by antibiotic-resistant *A. baumannii* in ICU adult patients. These data highlight the central role of interventions focused on antibiotic stewardship to control antibiotic resistant microorganism spreading and to prevent hospital outbreaks.

ERRATA CORRIGE

Ripubblichiamo di seguito un Abstract che per un disguido conteneva degli errori (Atti del 55° Congresso Nazionale SItI (Padova, 28 settembre - 1 ottobre, 2022) - J Prev Med Hyg 2022; 63 (Suppl. 1): E1-E443)

COMUNICAZIONI ORALI

MEDICINA DEL TURISMO E DELLE MIGRAZIONI

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Maternal and perinatal health among undocumented migrants: estimating health needs and healthcare coverage through national health management information systems at decentralized level

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BACKGROUND

Undocumented migrants experience poor maternal and perinatal health due to an underlying combination of increased health needs due to higher exposure and susceptibility to disease and risk factors, along with decreased healthcare coverage due to legal and socio-economic barriers including lack of/limited access to National Health Services, language, and poverty.

METHODS

This retrospective cross-sectional cohort study aimed to estimate maternal and perinatal health outcomes and healthcare coverage through maternity records from a sub-national Health Management Information System in Lombardy Region (Italy) from 2016 through 2020. Data was disaggregated by migrant status based on NHS temporary registration code, issued to undocumented migrants for access to essential and emergency care including maternity.

RESULTS

1595 undocumented migrant women and their babies were included in the study. Demographics and Socio-economics: Region of birth was Eastern Europe (35.1%), Africa (25.9%), Latin America (15.3%), Asia (8.9%); 7.3% undocumented migrants were employed, 45.2% married, 55.4% had no/ low schooling compared to 80.1%, 59% and 15.8% Italians. Obstetric history: age at delivery ≤ 25 was 14.2% in undocumented migrants and 7.1% in Italians, 30.2% undocumented migrants were primipara, < 1% had a previous abortion, and 14.4% a previous cesarean section. Antenatal care: 60.9% had ≥4 visits, 70.1% the first antenatal care visit ≤ 12 weeks of gestation, 66,2% had ≥ 2 ultrasound tests including one ≤ 12 weeks of gestation, 6,5% complete laboratory tests, compared to, 94.6%, 97.1%, 96.6%, and 74.2% for Italians. Intra-partum care: 99,2% deliveries were single and 95,2% had a normal fetal presentation; 68.6% deliveries were normal, 13.6% scheduled cesarean sections, 10.3% forceps, 4.5% vacuum extraction, 2.6% emergency cesarean section; episiotomy was conducted in 16.7% deliveries. Outcomes: 80% pregnancies were physiological, 4.8% presented intra-uterine growth retardation, 9.3% were pre-term, 17.2% small for gestational age, 7.2% had a low weight at birth, 1.4% a low Apgar score; 3,1% newborns presented malformations, 2.6% needed resuscitation, 49% initiated breastfeeding ≤ 2h after delivery; severe post-partum haemorrhage occurred in 3,5% deliveries.

CONCLUSIONS

Undocumented migrants experienced poor maternal and perinatal health. Their socio-economic and health indicators were consistently poor, especially from the Africa Region, showing vulnerability and inequality compared to regular migrants and Italians. Antenatal care is a major concern. Known risk factors including fragile socio-economic conditions along with legal and linguistic barriers to healthcare need to be addressed through tailored interventions including outreach health promotion focusing on safe motherhood and neonatal care, healthcare provider training, cultural mediation, translation, and functional language learning.

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